Notes on the Design of Bioequivalence Study: Efavirenz

Notes on the design of bioequivalence studies with products invited for submission 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 efavirenz.

Pharmacokinetics of efavirenz

Following oral administration, efavirenz peak plasma concentrations are typically reached within 5 h post-dose. Relative to fasting conditions, the administration of a single dose of efavirenz with a standardized high-fat meal increases the rate and extent of absorption of efavirenz. For this reason, efavirenz is to be administered on an empty stomach, preferably at bedtime.

Efavirenz is metabolized to a large extent via CYP3A and CYP2B6. The mean terminal half-life of efavirenz is 52–76 h following single doses and 40–55 h following multiple doses. Efavirenz is predominantly excreted via the bile and undergoes enterohepatic recycling.

Efavirenz appears to demonstrate non-linear pharmacokinetics with less than proportional increases in AUC observed with increasing dose, due to very limited solubility.

Guidance for the design of bioequivalence studies

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

**Dose:** As per Section 7.4.1.1 of Annex 7, TRS 992, for APIs with non-linear pharmacokinetics within the range of strengths due to limited solubility of the API and resulting in less than proportional increases in AUC with increasing dose, bioequivalence studies should be conducted on at least the lowest strength (or a strength in the linear range) and the highest strength of a series of strengths.

Efavirenz is marketed in the strengths of 50 mg, 200 mg and 600 mg (either as tablets or as capsules). For a series of strengths, the bioequivalence study should be conducted with the 600 mg and the 50 mg strength. An additional strength biowaiver for the 200 mg strength can be requested. Refer to Annex 7, TRS 992 for the requirements regarding this approach. A decision on the acceptability of the additional strength biowaiver request, however, can only be made upon review of the data submitted in the application.
**Fasting/fed:** The bioequivalence study(ies) should be conducted in the fasted state.

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

**Analytical considerations:** Efavirenz data should be the basis for the bioequivalence assessment. Assay sensitivity for efavirenz (limit of quantitation) is currently 50–100 ng/ml.

**Sample size:** Efavirenz is not a highly variable drug. Values for intra-subject %CV are generally 20–25% for C\(_{\text{max}}\) and 10–15% for AUC. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study. Study sample sizes for efavirenz studies are generally between 36 and 48, however, applicants are encouraged to perform individual sample size calculations for the bioequivalence study.

**Washout:** Taking into account the elimination half-life of efavirenz in the fasted state of 52–76 h, a washout period of 28–35 days is considered sufficient to prevent carry over.

**Blood sampling:** The blood sampling should be intensive during the first 5 hours after administration to properly characterize the C\(_{\text{max}}\) of efavirenz. Blood samples for the characterization of efavirenz pharmacokinetics should be taken for 72 h post-dose in order to determine truncated AUC values (AUC\(_{0-72h}\)).

**Parent or metabolite data for assessment of bioequivalence:** The parent drug is considered to best reflect the biopharmaceutical quality of the product. Therefore, bioequivalence should be based on the determination of efavirenz.

**Statistical considerations:** The data for efavirenz 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\(_{\text{max}}\) of the test to reference product should be within 80.00–125.00%.