Notes on the Design of Bioequivalence Study: Etravirine

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 can be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines of submission of documentation for WHO prequalification. In particular, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: Fifty-first report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva, World Health Organization, 2017. WHO Technical Report Series, No. 1003, Annex 6.

Below, additional specific guidance is provided on the invited immediate release products containing etravirine.

Pharmacokinetics of etravirine

The systemic exposure (AUC) to etravirine was decreased by about 50% when etravirine was administered under fasting conditions, as compared to administration following a meal. Therefore, etravirine should be taken following a meal. After oral administration with food, the maximum plasma concentration of etravirine is generally achieved within 4 hours. The terminal elimination half-life of etravirine was approximately 30-40 hours.

Guidance for the design of bioequivalence studies

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

Design: A single-dose crossover design is recommended.

Dose: As the EoI includes etravirine tablets of 100 mg and 200 mg, the bioequivalence study should be conducted with the highest strength.

Fasted/fed: The bioequivalence study should be conducted in the fed state with a standard breakfast, not a high-fat, high-calorie meal.

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 etravirine.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability for etravirine is around 22%. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: Taking into account the elimination half-life of etravirine of 30 – 40 h, a washout period of 14 days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive for the first four hours after administration to properly characterize the C_{max} of etravirine. As etravirine has a long elimination half-life, blood sampling should cover 72 hours after administration. For example, blood samples should be taken at pre-dose, 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 9.00, 12.00, 24.00, 48.00 and 72 h after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure etravirine in human plasma using LC-MS/MS analytical methodology with a LLOQ of 2 ng/ml. 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).

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

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72h}$ 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%.