Notes on the Design of Bioequivalence Study: Nevirapine

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. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, 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 oral liquid or powder for oral liquid containing nevirapine.

Pharmacokinetics of nevirapine

Nevirapine is readily absorbed (> 90%) after oral administration. Peak plasma nevirapine concentrations were attained by 4 hours following a single 200 mg dose. The absorption of nevirapine is not affected by food. The elimination half-life of nevirapine is approximately 45 hours.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of nevirapine, 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 50mg/5ml oral liquid or powder for oral liquid is the only invited strength, this strength should be employed. A dose of 200 mg is recommended.

Fasted/fed: Nevirapine oral suspension can be taken with or without food, therefore, a fasted state study is recommended.

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. Therefore, bioequivalence should be based on the determination of nevirapine.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability for nevirapine is around 12% for C_{max}. These data may facilitate the calculation of the sample size for the cross-over bioequivalence studies.

Washout: Taking into account the elimination half-life of nevirapine of 45 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 6 hours after administration to properly characterize the C_{max} of nevirapine. It is not necessary to take blood samples beyond 72 hours. For example, blood samples might be taken at pre-dose, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 24.00, 48.00, and 72.00 h after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure nevirapine in human plasma using LC-MS/MS analytical methodology with a LLOQ of 0.05 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 nevirapine should meet the following bioequivalence standards in each single-dose cross-over design study:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72h}$ of the test to comparator product should be within 80.00–125.00%
- The 90% confidence interval of the relative mean C_{max} of the test to comparator product should be within 80.00–125.00%.