Notes on the design of bioequivalence study: Mefloquine

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. 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 immediate release products containing mefloquine.

Pharmacokinetics of mefloquine

The maximum plasma concentration of mefloquine is reached within 6 to 24 hours after a single oral dose. The presence of food significantly enhances the rate and extent of absorption. The RBC concentration is almost twice as high as the plasma level.

The average elimination half-life of mefloquine in Caucasians is 21 days. Pharmacokinetic differences have been observed between various ethnic populations.

The tablets should be swallowed whole, preferably after a meal with plenty of liquid.

Guidance for the design of bioequivalence studies:

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

Design: A parallel design is recommended due to the long half-life of mefloquine. A cross-over design would require a wash out period of at least 100 days in principle.

Dose: As the EoI includes mefloquine 250 mg tablets only, this strength should be tested.

Fasted/fed: The bioequivalence study should be conducted in fed state.

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 mefloquine.

Sample size: Limited information is available on mefloquine variability. Mefloquine values for inter-subject variability seem to range between 35 to 44%. These data may facilitate the calculation of a sufficient sample size for the parallel bioequivalence study. However, a pilot study is recommended to confirm the inter-subject variability, to explore the optimal sampling times and to explore the feasibility of a cross-over design by investigating the intra-subject variability and the necessary wash-out period for a cross-over design.

Washout: Not applicable in case of a parallel design and in principle at least 100 days in case of a cross-over design. However, a shorter wash-out period could be feasible in the case of multiphasic elimination with most of the drug eliminated in the initial phases of elimination and plasma levels below 5% of C_{max} in the final phases of elimination.

Blood sampling: The blood sampling should be intensive around the 5.5 hours. It is not necessary to take samples after 72 hours. For example, blood samples might be taken at pre-dose and at 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 h after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure mefloquine 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). See Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information on bioanalytical recommendations.

Statistical considerations: The data for mefloquine should meet the following bioequivalence standards in a single-dose parallel or cross-over 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%.