Notes on the design of bioequivalence study: Amodiaquine

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 amodiaquine.

Pharmacokinetics of amodiaquine

Amodiaquine is quickly absorbed and converted into its main active form, desethylamodiaquine. The median amodiaquine T_{max} value is 0.91 h.

Amodiaquine is eliminated principally through biotransformation with only around 2% excreted unchanged in urine. Its elimination half-life is 24–28 hours.

When amodiaquine was taken with a high fat meal in healthy volunteers, the C_{max} and AUC_{0-t} of amodiaquine increased 23% and 58%, respectively, compared to that observed under fasted conditions. The C_{max} and AUC_{0-t} of the active metabolite desethylamodiaquine increased 18% and 12%, respectively, with a high-fat meal, compared to that observed under fasting conditions.

Guidance for the design of bioequivalence studies

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

Design: A single-dose cross-over design is recommended.

Dose: As the EoI includes amodiaquine 75 mg and 150 mg (or 76.5 mg and 153 mg) tablets co-blistered with sulfadoxine/pyrimethamine tablets, the 150 mg (or 153 mg) strength should be tested.

Fasted/fed: The bioequivalence study can be conducted in the fasted state as, although it is generally taken after meals, this seems to be related to tolerability.

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 amodiaquine.

Sample size: Amodiaquine values for intra-subject %CV have been reported to range between 25%-37% for C_{max} and 15%-30% for AUC. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: Taking into account the elimination half-life of amodiaquine of 28 h, a washout period of 2 weeks is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive in the first 2 hours since median T_{max} occurs before 1 hour. It is not necessary to take samples after 72 hours. For example, blood samples might be taken at pre-dose, and at 00.17, 00.25, 00.33, 00.50, 00.67, 00.83, 01.00, 01.25, 01.50, 01.75, 02.00, 02.50, 03.00, 03.50, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 24.00, 48.00 and 72.00 hours after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure amodiaquine 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).

Statistical considerations: The data for amodiaquine should meet the following bioequivalence standards in a single-dose 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%.

Information currently available to PQT/MED indicates that the comparator product is a highly variable drug product. Therefore, if the Applicant suspects that the variability of C_{max} or $AUC_{0\text{-}72h}$ is high (CV>30%), the applicant may prefer to employ a full replicate design study in order to widen the acceptance range of C_{max}. and/or $AUC_{0\text{-}72h}$. For more information on replicate study designs and widening the limits of average bioequivalence, refer to Section 7.9.3 of Annex 6, TRS 1003 and PQT/MED guidance document “Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED”.