Notes on the Design of Bioequivalence Study: Oral Artesunate

Notes on the design of bioequivalence studies with products invited to be submitted 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 artesunate.

Pharmacokinetics of artesunate

Artesunate is rapidly absorbed after oral administration. Most of the artesunate is promptly biotransformed, mainly through plasma esterases, into the active metabolite dihydroartemisinin (DHA). The median (range) artesunate $T_{\text{max}}$ value is 0.25 hours (0.25-1.33 h).

Artesunate has a plasma half-life of 3-29 minutes.

When artesunate was taken with a high fat meal in healthy volunteers, the $C_{\text{max}}$ and $AUC_{0-t}$ of artesunate decreased 66 and 13%, respectively, compared to that observed under fasting conditions. The $C_{\text{max}}$ and $AUC_{0-t}$ of the active metabolite dihydroartemisinin (DHA) decreased 48 and 5%, respectively, with a high-fat meal, compared to that observed under fasting conditions. Artesunate should not be taken with a high-fat, high-calorie meal.

Guidance for the design of bioequivalence studies

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

**Design:** A cross-over design is recommended.

**Dose:** As the EoI includes artesunate 25, 50, and 100 mg tablets, the bioequivalence study should be conducted with the highest strength of 100 mg if all strengths are developed and the requirements for the additional strength biowaiver are fulfilled.

**Fasting/fed:** The bioequivalence study should be conducted in the fasted state since artesunate should not be taken with a high-fat meal and, although it is generally taken after meals, this seems to be related to tolerability.

**Subjects:** Healthy adult subjects should be utilized. It is not necessary to include patients in the bioequivalence study.
Sample size: Artesunate C\textsubscript{max} seems to be highly variable (43 - 53% approx.). These data may facilitate the calculation of a sufficient sample size for a cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of artesunate in healthy volunteers of 3 - 29 minutes, a washout period of seven days is considered sufficient to prevent carry over.

Blood sampling: The blood sampling should be intensive for the first hours after administration to properly characterize the C\textsubscript{max} of artesunate. It is not necessary to take blood samples beyond 6 hours for the characterization of artesunate pharmacokinetics. For example, samples can be taken pre-dose and at 0.08, 0.16, 0.33, 0.50, 0.67, 0.83, 1.00, 1.16, 1.33, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00 and 6.00 hours.

Analytical considerations: Information currently available indicates that it is possible to measure artesunate 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\textsubscript{max} in most profiles of each formulation (test or comparator).

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. The disposition of artesunate should be characterized and the determination of bioequivalence will be based on the parent compound.

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

- The 90% confidence interval of the relative mean AUC\textsubscript{0-t} of the test to reference product should be within 80–125%.
- The 90% confidence interval of the relative mean C\textsubscript{max} of the test to reference product should be within 80–125%.

Information currently available to the PQTm suggests that the comparator product might be a highly variable drug product for C\textsubscript{max}, but not for AUC\textsubscript{0-t}. Widening of the acceptance range for C\textsubscript{max} might be acceptable if the applicant conducts a replicate cross-over study to estimate variability of the comparator product more accurately and the high variability of C\textsubscript{max} is demonstrated. For more information on replicate study designs and scaled average bioequivalence refer to Section 7.9.3 of Annex 6, TRS 1003.