Notes on the Design of Bioequivalence Study: Rectal 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 50, 100 and 200 mg artesunate rectal capsules.

**Pharmacokinetics of artesunate**

Following rectal administration, artesunate and its metabolite dihydroartemisinin (DHA), which is formed is rapidly by hydrolysis of the parent drug presumably through plasma/tissue esterases, are detectable in plasma beginning 0.25 to 0.5 hour after administration in most adult and pediatric patients. Concentrations of artesunate and DHA remain detectable for 3 to 5 hours while DHA can be observed for 3 to 12 hours in most human subjects.

Following rectal administration, Tmax for artesunate was reported to occur on average between 0.58 - 1.43 hours, and artesunate half-life was estimated at 0.9 - 0.95 hours. Following rectal administration of artesunate, DHA concentrations peaked between 1.13 - 2.0 hours, and DHA was eliminated with a half-life averaging 0.79 - 1.8 hours.

**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 single-dose cross-over design is recommended.

**Dose:** The EoI includes artesunate suppositories of 50 mg, 100 mg and 200 mg. Since the comparator product is available as a 100 mg strength, the proposed 100 mg strength should be employed in the bioequivalence study.

**Fasting/fed:** A fasting study is recommended to avoid stimulation of the gastrocolic reflex.

**Subjects:** Healthy adult subjects should be used. It is not necessary to include patients in the bioequivalence study.

**Sample size:** Information on rectal artesunate currently available to the PQTM indicates that the intra-subject variability for rectal artesunate is higher than 30% (40-50%). These data will facilitate the calculation of sufficient sample size for the bioequivalence study.
Washout: Taking into account that the elimination half-life of artesunate is 1 hour in healthy volunteers, a washout period of one week is considered sufficient to prevent carry over.

Blood sampling: As artesunate has a short half-life, blood sampling should be intensive in the first 2 hours after administration to properly characterize the Cmax of artesunate. It is not necessary to take blood samples beyond 12 hours.

Analytical considerations: Information currently available to the PQTm 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 Cmax 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 rate and extent of absorption for artesunate. The data for the parent compound(s) will be used to assess bioequivalence. Although the results of the parent compound will be used for the decision on bioequivalence, if data are available for the metabolite dihydroartemisinin, pharmacokinetic and statistical results for this metabolite should also be provided as it will help the WHO to understand the relationship between parent and metabolite, and will provide scientific knowledge in the area of decision-making.

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 of the test to reference product should be within 80–125%
- The 90% confidence interval of the relative mean Cmax of the test to reference product should be within 80–125%.

Information currently available to PQTm indicates that the comparator product is a highly variable drug product. Therefore, if the Applicant suspects that the variability of Cmax is high (CV>30%), the applicant may prefer to employ a replicate design study for at least the comparator product in order to scale the acceptance range of Cmax. For more information on replicate study designs and average scaled bioequivalence, refer to Section 7.9.3 of Annex 7, TRS 992.