Notes on the Design of Bioequivalence Study: Rectal Artesunate

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 rectal capsules containing artesunate.

Pharmacokinetics of artesunate

Following rectal administration, artesunate and its metabolite dihydroartemisinin (DHA), which is formed 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 paediatric 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, T_{max} for artesunate was reported to occur on average between 0.58 – 1.43 hours, and artesunate elimination 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.

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

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 artesunate.

Sample size: Information on rectal artesunate currently available to the PQT/MED indicates that the intra-subject variability for rectal artesunate is higher than 30% (40-50%). These data may 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 C_{max} of artesunate. It is not necessary to take blood samples beyond 12 hours.

Analytical considerations: Information currently available to the PQT/MED 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_{max} in most profiles of each formulation (test or comparator).

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_{0-t} 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-t} 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-t}. 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”.