Notes on the Design of Bioequivalence Study:
Artemether + Lumefantrine

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team: medicines 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 fixed-dose combination products, containing 20 mg artemether and 120 mg lumefantrine.

Pharmacokinetics of artemether

After oral administration, artemether peak plasma concentrations are reached after about two hours. Concomitant intake of a high fat meal enhances the absorption of artemether, resulting in an increase in the relative bioavailability by more than two-fold.

Artemether is rapidly and extensively metabolized (substantial first pass metabolism) into its main active metabolite, dihydroartemisinin. This metabolite is further converted to inactive metabolites. Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about two hours.

Pharmacokinetics of lumefantrine

After oral administration of lumefantrine, peak plasma concentrations are observed after about 6–8 hours. Concomitant intake of a high fat meal enhances the absorption of lumefantrine, resulting in an increase in the relative bioavailability by more than 16-fold. In patients with malaria, this increase was only two-fold, probably due to the lower fat content of the food ingested by acutely ill patients. Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Lumefantrine is metabolized into the active desbutyl-lumefantrine, however, the systemic exposure to this metabolite is low. Lumefantrine is eliminated very slowly with a terminal half-life of 2–3 days in healthy volunteers and 4–6 days in patients with falciparum malaria.
Guidance for the design of bioequivalence studies

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

Dose: A single oral dose (four tablets of artemether 20 mg + lumefantrine 120 mg) of each formulation (test or comparator) in each study period should be applied. The dose is in line with the recommended dose in adult patients.

Fasting/fed: As it is recommended to take the originator tablets with food, and the absorption is more variable if the tablets are taken in the fasted state, we recommend administration of the tablets with a standard breakfast, not a high-fat, high-calorie meal, as a standard breakfast is considered to be closest to real-life conditions in malaria patients.

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

Power: Information on artemether+lumefantrine currently available to the PQP indicates that the intra-subject variability for artemether is around 25%, and around 30% for lumefantrine. These data will facilitate the calculation of sufficient power for the bioequivalence study.

Washout: Taking into account the elimination half-life of lumefantrine in healthy volunteers (2–3 days), a washout period of at least two weeks is considered sufficient to prevent carry over.

Blood sampling: As artemether has a short half-life, blood sampling should be intensive in the first 8–10 hours after administration to cover the rate and extend of absorption of artemether. As lumefantrine has a long elimination half-life, blood sampling should cover 72 hours after administration. It is not necessary to take blood samples over a longer time period, as this will only substantiate the elimination phase lumefantrine.

Analytical method: Information currently available to the PQP indicates that it is possible to measure simultaneously artemether, dihydroartemisinin and lumefantrine in human plasma using LC-MS/MS analytical methodology. Care should be taken with sample treatment and pre-treatment (instability of the compound may be a problem), and the lower limit of quantification (LOQ), although the latter should not be a problem with the dose advised.

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the rate and extent of absorption for artemether as well as for lumefantrine. 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.