Notes on the Design of Bioequivalence Study: Sulfadiazine

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-seventh report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited immediate release products containing sulfadiazine.

Pharmacokinetics of sulfadiazine

Peak blood concentrations are reached within three to six hours. The serum half-life is 8 – 17 hours (mean 10 h) in healthy volunteers.

Guidance for the design of bioequivalence studies

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

Design: A single-dose crossover design is recommended.

Dose: As the EoI includes sulfadiazine tablets of 500 mg, the bioequivalence study should be conducted with this strength.

Fasted/fed: The bioequivalence study should be conducted in the fasted state.

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 sulfadiazine.

Sample size: There is no information in the literature on the intra-subject variability of sulfadiazine. A pilot study is recommended to estimate the intra-subject variability of the primary pharmacokinetic parameters. Therefore, conducting a pilot study is recommended to estimate the intra-subject variability of these pharmacokinetic parameters, which is necessary for the calculation of a sufficient sample size for a single dose cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of sulfadiazine of 10 (8 – 17) h, a washout period of 7 days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive for the first six hours after administration to properly characterize the C_{max} of sulfadiazine. For example, blood samples should be taken at pre-dose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 h after drug administration.

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