Notes on the Design of Bioequivalence Study: Diethylcarbamazine

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 diethylcarbamazine.

Pharmacokinetics of diethylcarbamezine

Diethylcarbamazine is absorbed almost completely by the oral route, reaching the maximum concentration 2–3 h after administration in fed state. Diethylcarbamazine tablets should preferably be administered after meals. The plasma half-life is generally 6–12 hours.

Guidance for the design of bioequivalence studies

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

Design: A single-dose cross-over design is recommended.

Dose: A single dose of 100 mg of diethylcarbamazine citrate should be employed in the bioequivalence study, as this is only diethylcarbamazine strength listed in the EoI.

Fasted/fed: The bioequivalence study should be conducted in the fed state as diethylcarbamazine is recommended to be taken with food. We recommend administration 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 patients.

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, the data for the parent compound should be used to assess bioequivalence of diethylcarbamazine...

Sample size: Diethylcarbamazine pharmacokinetics in fed state seems to display low variability (7–8%) for both C_{max} and AUC_{0-t}. A minimum sample size of 14 subjects is recommended to ensure a minimum of 12 subjects complete the study (in case of subject dropouts).

Washout: Taking into account the elimination half-life of diethylcarbamazine in healthy volunteers (about 12 h), a washout period of 7 days is considered sufficient to prevent carry over.

Blood sampling: The blood sampling should be intensive in the first four (4) hours after administration to properly characterize the C_{max} of diethylcarbamazine. It is not necessary to collect blood samples beyond 72 hours for the characterization of the pharmacokinetics of diethylcarbamazine.

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

BCS-based biowaiver: A BCS- based biowaiver for diethylcarbamazine is considered a possible alternative to a bioequivalence study, provided the requirements for granting a BCS-based biowaiver are met as outlined in the ICH Guideline "*Biopharmaceutics Classification System-Based Biowaivers*" M9 (2019) and the PQT/MED guidance "*PQT/MED-specific Annotations for the ICH M9 Guideline for Biopharmaceutics Classification System (BCS)-based Biowaiver Applications*" (2021).