Notes on the Design of Bioequivalence Study: Diethylcarbamazine

Notes on the design of bioequivalence studies with products invited for submission 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 diethylcarbamazine.

Pharmacokinetics of diethylcarbamazine
Diethylcarbamazine is absorbed almost completely by the oral route and diffuses widely into non-fatty tissues. Its metabolism is rapid and extensive with the residual fraction being recovered unchanged in the urine in the subsequent 48 hours. The plasma half-life is generally approximately 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:

**Dose:** A single dose of 100 mg of diethylcarbamazine citrate should be employed in the bioequivalence study.

**Fasting/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 used. It is not necessary to include patients in the bioequivalence study.

**Analytical considerations:** The measurement of diethylcarbamazine parent drug is feasible and it is considered to be more discriminative to differences in the biopharmaceutical performance of the drug products.
**Power:** Diethylcarbamazine pharmacokinetics in fed state seems to be low in variability (7–8%) for both $C_{\text{max}}$ and $AUC_T$. 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 seven days is considered sufficient to prevent carry over.

**Blood sampling:** The blood sampling of diethylcarbamazine should be intensive in the first four hours after administration to properly characterize the $C_{\text{max}}$ of diethylcarbamazine. It is not necessary to take blood samples beyond 72 hours for the characterization of diethylcarbamazine.

**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 will be used to assess bioequivalence.

**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 $AUC_T$ of the test to reference product should be within 80–125%.
- The 90% confidence interval of the relative mean $C_{\text{max}}$ of the test to reference product should be within 80–125%.

**BCS-based biowaiver:** Diethylcarbamazine is considered to be a highly soluble drug according to the Biopharmaceutics Classification System (BCS). Currently, diethylcarbamazine is considered to be a Class III API because definitive information demonstrating its complete absorption is lacking. Therefore, a BCS-based biowaiver application could be possible if:

a) The qualitative composition of excipients of the test product is the same as that of the comparator product (Supatonin);

b) The quantitative composition of excipients is very similar (and proportional due to the difference in strength) between test and comparator products; and

c) Dissolution profiles are very rapid (> 85% in 15 min) for both test and comparator product.

Refer to Annex 7, TRS 992 for more information.