Notes on the Design of Bioequivalence Study: Praziquantel

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 praziquantel.

Pharmacokinetics of praziquantel

Praziquantel is rapidly absorbed (80%) following oral administration with a Tmax of approximately 1–3 hours. When administered with food, the Cmax and AUC of praziquantel are higher relative to the fasting state, although the variability is also increased. Praziquantel should always be taken with food.

Praziquantel is rapidly and extensively metabolized (substantial first pass metabolism) into its main active metabolite. The terminal elimination half-life of praziquantel is approximately 0.8–3 hours when administered with food.

Guidance for the design of bioequivalence studies

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

Dose: A single oral dose of one tablet of praziquantel 600 mg should be feasible. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of Cmax in most profiles of each formulation (test or comparator).

Fasting/fed: The bioequivalence study should be conducted in the fed state as praziquantel is recommended to be taken with food. While specific requirements regarding the type of meal are not necessary, the variability is increased if the tablets are taken with a high-fat, high-calorie meal and hence, administration with a standard breakfast, not a high-fat, high-calorie meal, is recommended.

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

Power: Information on praziquantel currently available to the PQTm indicates that the intra-subject variability for praziquantel is around 50–60% for Cmax and 35% for AUCT. These data will facilitate the calculation of sufficient power for the bioequivalence study.
**Washout:** Taking into account the elimination half-life of praziquantel in healthy volunteers (approximately three hours), a washout period of seven days is considered sufficient to prevent carry over.

**Blood sampling:** The blood sampling for praziquantel should be intensive the first four hours after administration to properly characterize the $C_{\text{max}}$ of praziquantel. It is not necessary to take blood samples beyond 12 hours.

**Analytical considerations:** Information currently available to the PQTm indicates that it is possible to measure praziquantel in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the $C_{\text{max}}$ in most profiles of each formulation (test or comparator).

**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 praziquantel 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%.

Information currently available to PQTm indicates that the comparator product is a highly variable drug product. Therefore, if the Applicant suspects that the variability of $C_{\text{max}}$ is high (CV>30%), the applicant may prefer to employ a replicate design study for at least the comparator product in order to scale the acceptance range of $C_{\text{max}}$. For more information on replicate study designs and average scaled bioequivalence, refer to Section 7.9.3 of Annex 7, TRS 992.