

## Notes on the Design of Bioequivalence Study: Praziquantel

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-first report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*, Geneva: World Health Organization, 2017. WHO Technical Report Series, No. 1003, Annex 6.

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  $T_{max}$  of approximately 1–3 hours. When administered with food, the  $C_{max}$  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:

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

**Dose:** A single oral dose of one tablet of praziquantel 600 mg, which is the only one included in the EoI, should be administered.

**Fasted/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 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 praziquantel.

**Sample size:** Information on praziquantel currently available to the PQT/MED indicates that the intra-subject variability for praziquantel is around 50–60% for  $C_{max}$  and 35% for  $AUC_{0-t}$ . 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, a washout period of at least 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  $C_{max}$  of praziquantel. For example, samples should be taken at pre-dose, 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00 and 12:00 h after drug administration. It is not necessary to collect blood samples beyond 12 hours.

**Analytical considerations:** Information currently available to the PQT/MED 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  $C_{max}$  in most profiles of each formulation (test or comparator).

**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  $AUC_{0-t}$  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%.

Information currently available to PQT/MED indicates that the comparator product is a highly variable drug product. Therefore, if the Applicant suspects that the variability of  $C_{max}$  or  $AUC_{0-t}$  is high ( $CV > 30\%$ ), the applicant may prefer to employ a full replicate design study in order to widen the acceptance range of  $C_{max}$  and/or  $AUC_{0-t}$ . For more information on replicate study designs and widening the limits of average bioequivalence, refer to Section 7.9.3 of Annex 6, TRS 1003 and the PQT/MED guidance document “Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED”.