Notes on the Design of Bioequivalence Study:

Arpraziquantel

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. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, 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 arpraziquantel.

Pharmacokinetics of arpraziquantel

After oral administration, maximum plasma concentrations of arpraziquantel are reached within 2-3 hours. In adults, a positive food effect is observed with a higher arpraziquantel Cmax and AUC (296% and 167%, respectively) after dosing in the fed state compared to the fasting state. Arpraziquantel should be taken after a meal. The elimination half-life of unchanged arpraziquantel is approximately 3 hours.

Guidance for the design of bioequivalence studies

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

Design: A single-dose, crossover design is recommended.

Dose: The EoI includes 150 mg and 300 mg (scored) dispersible tablets. If both strengths are developed, a BE study comparing a single oral dose of 1 x 300 mg tablet (Test) vs. 2 x 150 mg (Comparator) should be completed. It may be possible to request an additional strength biowaiver for the lower strength.

When conducting bioequivalence studies, it is essential to administer the test and the comparator product according to their corresponding instructions for use. In those cases where the test and the comparator product are different dosage forms with different methods of administration (e.g., an orodispersible tablet that should be taken after wetting the mouth with 20 ml of water vs. a dispersible tablet to be dispersed in 30 – 50 mL of water prior to consumption) the bioequivalence study should be conducted employing the intended method of administration of each product. It is considered incorrect to standardize the volume of liquid in all these cases (e.g. administering a glass of water after the intake of a dispersible tablet or rinsing the container where a dispersible tablet has been suspended with the remaining liquid of a glass of water) because this standardization does not occur in real life conditions.

Fasted/fed: The bioequivalence study should be conducted in the fed state as arpraziquantel is recommended to be taken with food. 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 arpraziquantel.

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}. Similar values are expected for arpraziquantel. These data will facilitate the calculation of sufficient power for the bioequivalence study.

Washout: Taking into account the elimination half-life of arpraziquantel in healthy volunteers, a washout period of at least seven days is considered sufficient to prevent carry over.

Blood sampling: The blood sampling for arpraziquantel should be intensive the first four hours after administration to properly characterize the C_{max} of arpraziquantel. 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 arpraziquantel 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). See Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information on bioanalytical recommendations

Statistical considerations: The data for arpraziquantel 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 suggests that the comparator product is a highly variable drug product for both AUC_{0-t} and C_{max} in the fed state. 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 of the acceptance limits based on the intra-subject variability of the comparator product, refer to Section 7.9.3 of Annex 8, TRS 1052 and PQT/MED guidance document "Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED".