Notes on the Design of Bioequivalence Study: Albendazole

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 albendazole.

Pharmacokinetics of albendazole

Generally, the antihelminthic action of albendazole is intra-intestinal. However, at higher albendazole doses, sufficient amounts are absorbed and metabolised to the active sulphoxide metabolite to have a therapeutic effect against tissue parasites. Therefore, pharmacokinetic bioequivalence studies can be used to assess the biopharmaceutical quality of albendazole products, avoiding the necessity of conducting clinical trials to establish safety and efficacy.

In humans, the full extent of albendazole absorption following oral administration has not been established. However, it is known that albendazole is poorly absorbed with most of an oral dose remaining in the gastrointestinal tract. The poor absorption is believed to be due to the low aqueous solubility of albendazole. Absorption is significantly enhanced (approximately five-fold) if albendazole is administered with a fatty meal. Consequently, albendazole is to be taken concomitantly with food. The fat content of the food affects significantly the extent of absorption. Therefore, bioequivalence studies should be conducted in the fed state and the meal composition should be identical in both periods.

Albendazole rapidly undergoes extensive first-pass metabolism in the liver, but it can be detected in plasma. Albendazole sulfoxide is the primary metabolite, which is thought to be the active moiety in effectiveness against systemic tissue infections. The plasma half-lives of albendazole and albendazole sulfoxide are approximately 3 hours and 8.5 hours, respectively. Albendazole sulfoxide and its metabolites appear to be principally eliminated in bile, with only a small proportion appearing in the urine.

Guidance for the design of bioequivalence studies

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

Design: A single-dose replicate 4x2 crossover design is recommended, due to the high intra-subject variability observed in the comparator product, to estimate the intra-subject variability of the comparator product and to widen the acceptance range for C_{max} and AUC_T according to the variability of the comparator product.

Dose: As the EoI includes only albendazole 400 mg chewable tablets, this strength should be used in the bioequivalence study. During treatment albendazole tablets can be administered whole or chewed but, for the bioequivalence study, both products should be administered whole (unchewed).

Fastedg/fed: The bioequivalence study should be conducted in the fed state as albendazole is recommended to be taken with food, because of its increased bioavailability which depends on the fat content of the meal. Therefore, a standard / normal breakfast or a high-fat, high-calorie breakfast are acceptable as long as they are identical in both study periods. A standard breakfast closest to real-life conditions in patients is preferred.

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.

Sample size: Albendazole pharmacokinetics in the fed state is highly variable (up to 68% for C_{max} and 62% for AUC), based on information available to the PQT/MED. These data may facilitate the calculation of sufficient sample size for a single-dose crossover bioequivalence study.

Washout: Taking into account the elimination half-life of albendazole and albendazole sulfoxide in healthy volunteers (about 3 and 8.5 hours, respectively), a washout period of seven days is considered sufficient to prevent carry over.

Blood sampling: The blood sampling for albendazole should be intensive the first four hours after administration to properly characterize the C_{max} of albendazole. It is not necessary to take blood samples beyond 18 hours for the characterization of albendazole pharmacokinetics.

Analytical considerations: Information currently available to the PQT/MED indicates that it is possible to measure albendazole 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 albendazole should meet the following bioequivalence standards in a single-dose cross-over design study:

- The 90% confidence interval of the relative mean AUC_T of the test to comparator product should be within 80.00 – 125.00%
- The 90% confidence interval of the relative mean C_{max} of the test to comparator 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_T and C_{max} in the fed state. Widening of the acceptance range for AUC_T for albendazole will be accepted by PQT/MED. Therefore, the applicant may design a replicate crossover study to estimate variability more accurately and to widen the acceptance range for C_{max} and AUC_T. For more information on replicate study designs and widening of the acceptance range based on the intra-subject variability of the comparator product, refer to Section 7.9.3 of Annex 8, TRS 1052. If widening of the acceptance range is planned for the AUC_T parameter, the principles described for C_{max} in Section 7.9.3 will apply and a four period, full replicate design study should be conducted to demonstrate bioequivalence, in order to assess the variability associated with each product.