Notes on the Design of Bioequivalence Study: Albendazole

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 albendazole.

Pharmacokinetics of albendazole

Generally, the antihelminthic action of albendazole is intra-intestinal. However, at higher albendazole doses, sufficient amounts are absorbed and metabolized to active the 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 sulphoxide 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:

Dose: Due to the low solubility of albendazole, the maximum applied strength (i.e. 400 mg for the 200 mg and 400 mg strengths) 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).
**Fasting/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 used. It is not necessary to include patients in the bioequivalence study.

**Analytical considerations:** The measurement of albendazole parent drug is feasible (LLOQ of at least 5 ng/mL) and it is considered to be more discriminative to differences in the biopharmaceutical performance of the drug products, even if the metabolite seems to be the active fraction.

**Power:** Albendazole pharmacokinetics in the fed state seem to be highly variable (40–60%) in both C\textsubscript{max} and AUCT, based on a pilot study available to the PQTm, where the products were administered with a normal breakfast and a high-fat, high-calorie breakfast. These data will facilitate the calculation of sufficient power for the 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\text{max} of albendazole. It is not necessary to take blood samples beyond 18 hours for the characterization of albendazole pharmacokinetics.

**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 albendazole should meet the following bioequivalence standards in a single-dose, crossover design study:

- The 90% confidence interval of the relative mean AUCT 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 suggests that the comparator product is a highly variable drug product for both AUCT and C\text{max} in the fed state. Widening of the acceptance range for AUCT for albendazole will be accepted by PQTm. Therefore, the applicant may design a replicate cross-over study to estimate variability more accurately and to widen the acceptance range for C\text{max} and AUCT. For more information on replicate study designs and average scaled bioequivalence, refer to Section 7.9.3 of Annex 7, TRS 992. If scaling is planned for the AUCT parameter, the principles described for C\text{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.