Notes on the Design of Bioequivalence Study: Mebendazole

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team: medicines 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 mebendazole.

Pharmacokinetics of mebendazole

Following oral administration, <10% of the dose reaches the systemic circulation due to incomplete absorption and extensive pre-systemic metabolism (first-pass effect). However, as absorption does occur, systemic levels obtained following administration of a product need to be assessed for reasons of safety. To this end, pharmacokinetic bioequivalence trials are considered the best way to assess the biopharmaceutical quality of a multisource mebendazole product, thus avoiding the need to conduct full clinical trials to establish the safety and efficacy of the proposed mebendazole product.

Maximum plasma concentrations are generally seen 2 - 4 hours after administration. Dosing with a high fat meal leads to a modest increase in the bioavailability of mebendazole.

Orally administered mebendazole is extensively metabolised primarily by the liver. Plasma concentrations of its major metabolites (amino and hydroxylated amino forms of mebendazole) are substantially higher than those of mebendazole. Impaired hepatic function, impaired metabolism, or impaired biliary elimination may lead to higher plasma levels of mebendazole.

Mebendazole, the conjugated forms of mebendazole, and its metabolites likely undergo some degree of enterohepatic recirculation and are excreted in the urine and bile. The apparent elimination half-life after an oral dose ranges from 3–6 hours in most patients.

During chronic dosing (e.g., 40 mg/kg/day for 3–21 months), plasma concentrations of mebendazole and its major metabolites increase, resulting in approximately three-fold higher exposure at steady-state compared to single dosing.

Guidance for the design of bioequivalence studies

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

**Dose:** Due to the low solubility of mebendazole, the maximum applied strength (i.e., 500 mg for the 100 mg and 500 mg strengths) should be employed in the bioequivalence study. During treatment mebendazole tablets can be administered whole or chewed but, for the bioequivalence study, both products should be administered whole (unchewed).

**Fasting/fed:** The instructions for administration of mebendazole in its labeling do not indicate the need for administration with food because its indications are limited to local action, in contrast to albendazole. However, as a high fat meal seems to increase systemic exposure modestly, a study in the fed state is recommended.

**Subjects:** Healthy adult subjects should be utilized. It is not necessary to include patients in the bioequivalence study.
**Analytical considerations:** The measurement of the mebendazole in plasma is preferred as a better reflection on local availability at the site of action in the gastrointestinal lumen.

**Power:** There is no data available on the intra-subject variability of mebendazole, therefore a pilot study or a two-stage design is recommended. It is expected to be highly variable due to its limited and erratic absorption.

**Washout:** Taking into account the elimination half-life of approximately six hours, a washout period of seven days is sufficient to prevent carry over.

**Blood sampling:** The blood sampling for mebendazole should be intensive for the first four hours after administration to properly characterize the $C_{\text{max}}$ of mebendazole. It is not necessary to take blood samples beyond 32 hours.

**Parent or metabolite data for assessment of bioequivalence:** The parent drug is considered to best reflect the rate of release of the drug from the dosage form to the site of action in the lumen of the gastrointestinal tract. The data for the parent compound will be used to assess bioequivalence.

**Statistical considerations:** The data for mebendazole 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%.

If the applicant suspects that the variability of $C_{\text{max}}$ or $AUC_{T}$ is high (CV>30%), 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 $AUC_{T}$. Please note that widening of the acceptance range for $AUC_{T}$ for mebendazole will be accepted by PQTM. 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 $AUC_{T}$ 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.