

Notes on the design of bioequivalence study: Ethionamide

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 ethionamide.

Pharmacokinetics of ethionamide

Ethionamide maximum concentrations are observed one hour after administration of a single oral dose of 250 mg. C_{max} is expected to be approximately 2.16 mcg/ml. The mean (SD) half-life observed following a 250 mg oral dose was 1.92 (0.27) hours.

Ethionamide tablets may be administered without regard to the timing of meals.

Guidance for the design of bioequivalence studies:

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

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

Dose: As the EoI includes a 125 mg dispersible tablet and a 250 mg film-coated tablet, a 250 mg dose is recommended for the bioequivalence study since only the 250 mg strength is available for the comparator. In the case of the 125 mg dispersible tablet, a dose of 2 x 125 mg should be tested and the test product should be administered with the method of administration and volume of water intended for the dosing instructions of the proposed product, and compared with the reference tablet, which should be taken with 240 ml of water.

Fasted/fed: The bioequivalence study should be conducted in the fasted state because it can be taken without regard to food.

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 ethionamide.

Sample size: Ethionamide pharmacokinetic parameters, C_{\max} and AUC_{0-t} , in the fasting state seem to display low to moderate variability (16–28%), based on information available to the PQT/MED. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: Taking into account the elimination half-life of ethionamide of 2 h, a wash-out period of 7 days is considered sufficient to prevent carry over.

Blood sampling: The blood sampling should be intensive during the first three hours after administration. For example, samples should be taken at pre-dose, 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, and 24.00 h after drug administration.

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