Notes on the design of bioequivalence study: Ethionamide

Notes on the design of bioequivalence studies with products invited to be submitted 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 ethionamide.

Pharmacokinetics of ethionamide

Ethionamide maximum concentrations are observed one (1) hour after administration of a single oral dose of 250 mg. Cmax 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 cross-over design is recommended.

**Dose:** As the EoI includes 125 mg and 250 mg strengths, the 250 mg strength is recommended for the bioequivalence study. A dose of 1 x 250 mg or 2 x 125 mg should be tested. In the case of the 125 mg dispersible tablet, 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.

**Fasting/fed:** The bioequivalence study should be conducted in the fasting state

**Subjects:** Healthy volunteers

**Sample size:** Ethionamide pharmacokinetic parameters, Cmax and AUC0-t, in the fasting state seem to possess low to moderate variability (16-28%), based on information available to the PQTm. These data will facilitate the calculation of a sufficient sample size for the bioequivalence study.

**Washout:** At least 7 days.

**Blood sampling:** Predose, 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 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 $C_{\text{max}}$ in most profiles of each formulation (test or comparator).

**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.

**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 80-125%.

- The 90% confidence interval of the relative mean $C_{\text{max}}$ of the test to reference product should be within 80-125%.