Notes on the Design of Bioequivalence Study: Norethisterone

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 norethisterone.

Pharmacokinetics of norethisterone

Norethisterone, also known as norethindrone, is rapidly and completely absorbed after oral administration. Peak plasma concentrations occur between 1 and 3 hours. The half-life of elimination varies from 5 to 12 hours, with a mean of 7.6 hours.

Guidance for the design of bioequivalence studies

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

Design: A single-dose crossover design is recommended.

Dose: As the EoI includes norethisterone 350 micrograms tablets, the bioequivalence study should be conducted with this strength.

Fasted/fed: As norethisterone can be taken with or without food, a fasted state study is recommended.

Subjects: Healthy adult female (non-pregnant, non-lactating) 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 norethisterone

Sample size: Norethisterone C_{max} seems to be moderately variable (15% approx.). These data may facilitate the calculation of a sufficient sample size for a cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of norethisterone in healthy volunteers of 5 – 12 hours, a washout period of 7 days is considered sufficient to prevent carry over.

Blood sampling: The blood sampling should be intensive for the first hours after administration to properly characterize the C_{max} of norethisterone. It is not necessary to take blood samples beyond 36 hours for the characterization of the pharmacokinetics of norethisterone. For example, samples can be taken pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 24.00 and 36.00 hours.

Analytical considerations: Information currently available indicates that it is possible to measure norethisterone in human plasma using LC-MS/MS analytical methodology (LLOQ = 50 pg/ml). 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). See Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information on bioanalytical recommendations.

Statistical considerations: The data for norethisterone should meet the following bioequivalence standards in a single-dose crossover design study:

- The 90% confidence interval of the relative mean AUC_{0-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%.