Notes on the Design of Bioequivalence Study: Etonogestrel implant

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. In particular, 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 prolonged release implant containing etonogestrel.

Pharmacokinetics of etonogestrel

After the insertion of the implant, etonogestrel is rapidly absorbed into the circulation. Ovulation-inhibiting concentrations are reached within 1 day. Maximum serum concentrations (between 472 and 1,270 pg/ml) are reached within 1 to 13 days. The release rate of the implant decreases with time. As a result, serum concentrations decline rapidly over the first few months. By the end of the first year, a mean concentration of approximately 200 pg/ml (range 150-261 pg/ml) is measured, which slowly decreases to 156 pg/ml (range 111-202 pg/ml) by the end of the third year.

Guidance for the design of bioequivalence studies

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

Design: A single-dose parallel design is recommended.

Dose: As the EoI includes etonogestrel implant containing 68 mg of etonogestrel, the bioequivalence study should be conducted with this product strength.

Fasted/fed: N/A.

Subjects: Healthy adult female 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 etonogestrel.

Sample size: Etonogestrel C_{max} and C_{τ} inter-subject variability seems to be around 47% and 52%. These data may facilitate the calculation of a sufficient sample size for a single dose parallel bioequivalence study.

Washout: N/A.

Blood sampling: The blood sampling should be intensive for the first two weeks after administration to properly characterize the C_{max} of etonogestrel. For example, samples can be taken pre-dose and 1, 3, 5, 7, 9, 11, 13, 15 ,17, 21 and 28 days after implant insertion and 2, 4, 6, 8, 10, 12, 15, 18, 21, 24, 27, 30, 33 and 36 months after insertion.

Analytical considerations: Information currently available indicates that it is possible to measure etonogestrel in human plasma using LC-MS/MS analytical methodology (e.g., 30 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 etonogestrel should meet the following bioequivalence standards in a single-dose parallel design study:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}t}$ 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%.
- The 90% confidence interval of the relative mean $C\tau$ ($C_{3\ years}$) of the test to comparator product should be within 80.00 – 125.00%.
- The 90% confidence interval of the relative mean $AUC_{0\text{-}1\ year}$, $AUC_{1\text{-}2\ years}$ and $AUC_{2\text{-}3\ years}$ should be submitted as supportive information.