

Notes on the Design of Bioequivalence Study: Levonorgestrel intra-uterine system

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team – Medicines (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-first Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2017. WHO Technical Report Series, No. 1003, Annex 6.

Below, additional specific guidance is provided on the invited intra-uterine system containing levonorgestrel.

Pharmacokinetics of levonorgestrel

Levonorgestrel is delivered from the intra-uterine system directly into the uterine cavity. Plasma levonorgestrel concentrations of 276 ± 119 pg/ml, 196 ± 87 pg/ml and 177 ± 70 pg/ml at 56 weeks, 24 months and 48 months have been observed, respectively. A half-life of 20 hours is considered the best estimate although some studies have reported values as short as 9 hours and others as long as 80 hours. Another important finding, although one in agreement with experience with other synthetic steroids, has been marked differences in metabolic clearance rates among individuals, even when administration was by the intravenous route.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of levonorgestrel intra-uterine system 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 the intrauterine system with reservoir containing 52 mg of levonorgestrel, the bioequivalence study should be conducted with this product.

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. Therefore, bioequivalence for levonorgestrel should be based on the determination of the parent compound.

Sample size: Levonorgestrel C_{\max} inter-subject variability seems to be around 35 – 45%. 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 days after administration to properly characterize the C_{\max} of levonorgestrel. For example, samples can be taken pre-dose and 1, 3, 5, 7, 9, 11, 13, 14, 15, 17, 19, 21, 23, 25 and 27 days after injection as well as 3 and 6 months after injection and 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 years after injection.

Analytical considerations: Information currently available indicates that it is possible to measure levonorgestrel in human plasma using LC-MS/MS analytical methodology (e.g., 15 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).

Statistical considerations: The data for levonorgestrel should meet the following bioequivalence standards in a single-dose parallel 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%.
- The 90% confidence interval of the relative mean C_{τ} ($C_{5 \text{ years}}$) of the test to comparator product should be within 80.00 – 125.00%.
- The 90% confidence interval of the relative mean $AUC_{0-1 \text{ year}}$, $AUC_{1-2 \text{ years}}$, $AUC_{2-3 \text{ years}}$, $AUC_{3-4 \text{ years}}$ and $AUC_{4-5 \text{ years}}$ should be submitted as supportive information.