Notes on the Design of Bioequivalence Study: Progesterone vaginal ring

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 prolonged release vaginal ring containing progesterone.

Pharmacokinetics of progesterone

Progesterone is extensively metabolized after oral administration during the first pass effect and its half-life is 16.8 ± 2.8 h. The vaginal route of administration circumvents the gastrointestinal and hepatic first pass effect. After the insertion of a vaginal ring, the concentrations of progesterone increase sharply and maximum concentrations are achieved during the first 1 – 3 days, subsequently the plasma concentrations decrease gradually with levels around 10 nmol/L after 16 weeks.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of progesterone contained in vaginal rings, the following guidance with regard to the study design should be taken into account:

Design: A single-dose parallel or crossover design is recommended.

Dose: As the EoI includes progesterone-releasing vaginal rings, containing 2.074 g of micronized progesterone, 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 progesterone should be based on the determination of the parent compound.

Sample size: The inter-subject and intra-subject variability of the pharmacokinetic parameters of progesterone (C_{max} and AUC_{0-t}) obtained with progesterone-releasing vaginal ring has not been described in the literature. Therefore, conducting a pilot study is recommended to optimize sampling times and estimate the inter-subject or intra-subject variability of these pharmacokinetic parameters, which is necessary for the calculation of a sufficient sample size for a single dose parallel and cross-over bioequivalence study, respectively.

Washout: N/A for parallel design. For a crossover design, a washout period of one menstrual cycle is recommended.

Blood sampling: The blood sampling should be intensive for the first days after administration to properly characterize the C_{max} of progesterone. For example, samples can be taken pre-dose and 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.5, 4.0, 5.0, 6.0, 9.0, 12.0, 18.0, 24.0, 30.0, 45.0, 60.0, 75.0, 90.0, 105.0 and 120.0 days after insertion.

Analytical considerations: Information currently available indicates that it is possible to measure progesterone in human plasma using LC-MS/MS analytical methodology, taking into account that progesterone is an endogenous compound and blank plasma to prepare calibration standards and QC samples with interfering endogenous progesterone levels below 20% of the necessary LLOQ may not be available. 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 progesterone should meet the following bioequivalence standards in a single-dose parallel design study:

- The 90% confidence interval of the relative mean $AUC_{0-3\ months}$ of the test to comparator product should be within 80.00 – 125.00%.
- The 90% confidence interval of the relative mean $AUC_{0-4\ months}$ 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 $C_{3\ months}$ of the test to comparator product should be within 80.00 – 125.00%.
- The 90% confidence interval of the relative mean $C_{4\ months}$, $AUC_{0-1\ month}$, $AUC_{1-3\ months}$, $AUC_{1-4\ months}$ of the test to comparator product should be submitted as supportive information.