Notes on the Design of Bioequivalence Study: Dapivirine

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-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 vaginal ring containing dapivirine.

Pharmacokinetics of dapivirine

Dapivirine is released from the ring in a sustained manner, distributed into vaginal fluid, and absorbed into surrounding tissues and plasma. Measurable dapivirine concentrations were detected in vaginal fluid and plasma within 1 to 4 hours after ring insertion. Concentrations of dapivirine in vaginal fluid exceeding the in vitro HIV-1 IC99 by 1000-fold are achieved within 24 hours of ring insertion. At 4 to 24 hours after ring insertion, vaginal fluid concentrations (at all 3 sampling locations: cervix, ring area, and introitus) are similar to those on Day 28 after continuous ring use. Dapivirine plasma concentrations at 24 hours after ring insertion are also similar to those at 28 days after continuous ring use. Systemic concentrations of dapivirine observed in plasma with the use of the Dapivirine Vaginal Ring were low (< 2 ng/mL).

Guidance for the design of bioequivalence studies

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

Design: A single-dose crossover design is recommended, although a parallel design is also acceptable.

Dose: As the EoI includes dapivirine silicone matrix vaginal ring containing 25 mg of dapivirine, 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. The data for the parent compound should be used to assess bioequivalence of dapivirine.

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

Washout: A washout period of one menstrual cycle is recommended.

Blood sampling: The blood sampling should be more frequent for the first days after administration to properly characterize the ascending levels of dapivirine. For example, samples can be taken pre-dose and 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0, 18.0, 20.0, 22.0, 24.0 and 28.0 days after insertion.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure dapivirine in human plasma using LC-MS/MS analytical methodology with a LLOQ of 20 pg/ml, but this sensitivity should be improved. 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 dapivirine should meet the following bioequivalence standards in a single-dose study:

- The 90% confidence interval of the relative mean C_{max} of the test to reference product should be within 80.00– 125.00%.
- The 90% confidence interval of the relative mean $AUC_{0\text{-}28\ days}$ of the test to reference product should be within 80.00–125.00%
- The 90% confidence interval of the relative mean $AUC_{0\text{-}14\ days}$ of the test to reference product should be within 80.00– 125.00%.
- The 90% confidence interval of the relative mean $AUC_{14\text{-}28\ days}$ of the test to reference product should be within 80.00– 125.00%.
- The 90% confidence interval of the relative mean $C_{28\ days}$ of the test to reference product should be within 80.00– 125.00%.
- The 90% confidence interval of the relative mean residual levels in the used rings of the test to reference product should be within 80.00– 125.00%.