Notes on the Design of Bioequivalence Study: Ulipristal acetate

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 immediate release products containing ulipristal acetate.

Pharmacokinetics of ulipristal acetate

Following oral administration of a single 30 mg dose, ulipristal acetate is rapidly absorbed, with a peak plasma concentration of 176 ± 89 ng/ml occurring approximately 1 hour (0.5-2.0 h) after ingestion, and with an $AUC_{0\text{-}inf}$ of 556 ± 260 ng.h/ml.

Administration of ulipristal acetate together with a high-fat breakfast resulted in approximately 45% lower mean C_{max}, a delayed T*max* (from a median of 0.75 hours to 3 hours) and 25% higher mean $AUC_{0\text{-}inf}$ compared with administration in the fasted state. The tablet can be taken with or without food.

The terminal half-life of ulipristal acetate in plasma following a single 30 mg dose is estimated to 32.4 ± 6.3 hours.

Guidance for the design of bioequivalence studies

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

Design: A single-dose cross-over design is recommended.

Dose: As the EoI includes 30 mg tablets, the bioequivalence study should be conducted with this strength.

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

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 ulipristal acetate should be based on the determination of the parent compound.

Sample size: Ulipristal acetate C_{max} seems to be moderately variable (27 – 30 %). 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 ulipristal acetate in healthy volunteers of 32 hours, a washout period of 21 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 Ulipristal acetate. It is not necessary to take blood samples beyond 72 hours for the characterization of the pharmacokinetics of immediate release products containing drugs with long half-lives. 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, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00, and 72.00 hours.

Analytical considerations: Information currently available indicates that it is possible to measure ulipristal acetate in human plasma using LC-MS/MS analytical methodology (e.g., 0.2 ng/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 ulipristal acetate 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%.