

Notes on the Design of Bioequivalence Study: Medroxyprogesterone acetate / Estradiol Cypionate

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 injectable products containing medroxyprogesterone acetate and estradiol cypionate.

Pharmacokinetics of medroxyprogesterone acetate and estradiol cypionate

Intramuscular medroxyprogesterone acetate and estradiol cypionate injection is a long acting injectable due to its slow absorption from the injection site. Estradiol cypionate is of medium-term action since, for about 15 days, it produce high serum levels, which subsequently decline resulting in uterine bleeding about 3 weeks after the injection. The prolonged release injectable containing 25 mg of medroxyprogesterone acetate and 5 mg of estradiol cypionate shows maximum concentrations 3 – 4 days after administration for medroxyprogesterone acetate and 2 – 3 days after administration for estradiol, but t_{max} might have occurred earlier since earlier samples were not taken in those studies. The apparent elimination half-life is 14 – 17 days for medroxyprogesterone acetate and 8 – 10 days for estradiol. Residual plasma levels of medroxyprogesterone remain detectable for up to 84 – 90 days after dosing.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of medroxyprogesterone acetate and estradiol cypionate 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 medroxyprogesterone acetate / estradiol cypionate, injection 25 mg / 5 mg, the bioequivalence study should be conducted with this strength.

Fasted/fed: N/A.

Subjects: Healthy adult females 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 drugs are considered to best reflect the biopharmaceutical quality of the product. However, estradiol cypionate is hydrolysed to release gradually

estradiol. Therefore, bioequivalence for medroxyprogesterone acetate and estradiol cypionate should be based on the determination of the medroxyprogesterone and estradiol.

Sample size: Estradiol C_{max} seems to exhibit inter-subject variability between 30 and 50% and medroxyprogesterone acetate C_{max} between 25 and 35%. These data may facilitate the calculation of a sufficient sample size for a parallel bioequivalence study.

Washout: N/A.

Blood sampling: Blood sampling needs to be undertaken frequently during the first days to characterise C_{max} adequately and up to 72 days after the day of injection. A possible sampling scheme could be: pre-injection, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 10.0, 12.0, 14.0, 16.0, 18.0, 21.0, 24.0, 28.0, 36.0, 48.0 and 72.0 days.

Analytical considerations: Information currently available indicates that it is possible to measure medroxyprogesterone acetate and estradiol in human plasma using LC-MS/MS analytical methodology (e.g., 20 and 1.0 pg/ml, respectively). 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 medroxyprogesterone acetate and estradiol should meet the following bioequivalence standards in a single-dose parallel design study:

- The 90% confidence interval of the relative mean $AUC_{0-28 \text{ days}}$ of the test to comparator product should be within 80.00 – 125.00%.
- 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 AUC_{0-inf} 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 AUC_{28-t} of the test to comparator product should be submitted as supportive information.