Notes on the Design of Bioequivalence Study: Medroxyprogesterone acetate

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-seventh Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited prolonged release injectable products containing medroxyprogesterone acetate.

Pharmacokinetics of medroxyprogesterone acetate

Intramuscular medroxyprogesterone acetate (MPA) is a long-acting injectable due to its slow absorption from the injection site. A 150 mg dose is first detectable in the blood 30 minutes after injection. After injection of 150 mg in the gluteal muscle, C_{max} was 4.49 ng/ml with a coefficient of variation (CV) of 58.7% for the reference product, and C_{max} of the test was 4.84 ng/ml with a CV of 85.8%. T_{max} was 6.76 days and 4.93 days, respectively, but in other studies t_{max} has been observed after 13 days. The concentration of medroxyprogesterone acetate decreases exponentially until it becomes undetectable (< 100 pg/ml) between 120−200 days following injection. At lower doses, plasma levels of MPA appear directly related to the dose administered. Plasma half-life is about six weeks (36.05 days and 44.03 days, respectively) after a single intramuscular injection.

MPA absorption from the SC injection site to achieve therapeutic levels is relatively prompt. The mean t_{max} is attained approximately one week after injection. The peak MPA concentrations (C_{max}) generally range from 0.5 to 3.0 ng/ml with a mean C_{max} of 1.5 ng/mL after a single SC injection. DMPA was administered subcutaneously into the anterior thigh or the abdomen to evaluate effects on MPA concentration-time profile. MPA trough concentrations (C_{min}; Day 91) were similar for the two injection locations, suggesting that injection site does not negatively affect the contraceptive efficacy. Residual MPA concentrations at the end of the dosing interval (3 months) of DMPA subcutaneous injection are generally below 0.5 ng/ml, consistent with its apparent terminal half-life of ~40 days after SC administration. Based on single-dose data, there was no evidence of non-linearity over the dose range of 50 to 150 mg after SC administration. The relationship between the AUC or the C_{min} and the SC dose of MPA appeared to be linear. The mean C_{max} did not change substantially with increasing dose.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of medroxyprogesterone acetate 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 150 mg/ml depot injection for intramuscular administration and the 104 mg/0.65 ml depot injection for subcutaneous administration, a bioequivalence study should be conducted for each strength and route of administration.

Fasted/fed: N/A.

Subjects: Healthy, adult, non-pregnant 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 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 medroxyprogesterone acetate.

Sample size: Medroxyprogesterone acetate C_{max} and partial AUCs seems to exhibit inter-subject variability around 40%. However, values of 60% or 85% have also been observed. These data may facilitate the calculation of a sufficient sample size for a parallel bioequivalence study. At least 60 subjects per arm are required for a power of 80% under the assumption of no treatment differences and 40% inter-subject CV.

Washout: N/A.

Blood sampling: Blood sampling needs to be undertaken up to 140 days after the day of injection. A possible sampling scheme could be: pre-injection, 0.083, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10.0, 12.0, 14.0, 16.0, 18.0, 21.0, 24.0, 28.0, 35.0, 49.0, 63.0, 77.0, (91.0 days for the IM injection / 98.0 days for the SC injection), 105, 119, and 140 days.

Analytical considerations: Information currently available indicates that it is possible to measure medroxyprogesterone acetate in human plasma using LC-MS/MS analytical methodology (e.g., 25 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) for medroxyprogesterone acetate. See Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information on bioanalytical recommendations.

Statistical considerations: The data for medroxyprogesterone acetate should meet the following bioequivalence standards in a single-dose parallel design study:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}91\ days}$ (IM) or $AUC_{0\text{-}98\ days}$ (SC) of the test to comparator product should be within 80.00 – 125.00%.
- The 90% confidence interval of the relative mean $AUC_{0\text{-}140\ days}$ 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 $AUC_{0\text{-}inf}$, $AUC_{0\text{-}21\ days}$, $AUC_{21\text{-}45\ days}$ and $AUC_{45\text{-}91\ days}$ (IM) or $AUC_{45\text{-}98\ days}$ (SC) of the test to comparator product should be submitted as supportive information.