Notes on the Design of Bioequivalence Study:

Moxidectin

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 may be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines on submission of documentation for WHO prequalification. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, 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 immediate release tablet containing moxidectin.

Pharmacokinetics of moxidectin

Following oral administration, maximum moxidectin plasma concentrations are observed around 3 h after dosing in the fasting state. AUC and C_{max} increase dose proportionally over the dose range of 2– 36 mg. The elimination half-life of orally administered moxidectin is about 23 days.

After administration of moxidectin with food, C_{max} and AUC increased 34 and 39%, respectively, however, this was not considered to be clinically relevant. Therefore, moxidectin may be administered with or without food.

Guidance for the design of bioequivalence studies

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

Design: A single-dose parallel study is recommended, considering the long elimination half-life.

Dose: As the 2 mg tablet is the only invited strength, this strength should be employed in the bioequivalence study.

Fasted/fed: In clinical practice, moxidectin may be taken without regard to food intake. A fasted state study is recommended.

Subjects: Healthy adult 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 moxidectin.

Sample size: Information currently available to PQT/MED indicates that the inter-subject variability for moxidectin is around 25% for C_{max} and AUC. These data may facilitate the calculation of the sample size for the parallel bioequivalence study.

Washout: Considering the elimination half-life of moxidectin (23 days), a parallel study design is recommended. A washout is not applicable.

Blood sampling: The blood sampling should be intensive for the first 5 hours after administration to properly characterize the C_{max} of moxidectin. It is not necessary to take blood samples beyond 72 hours. For example, blood samples might be taken at pre-dose, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00, 48.00, and 72.00 h after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure moxidectin in human plasma using LC-MS/MS analytical methodology with a LLOQ of 0.1 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). 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 moxidectin should meet the following bioequivalence standards in the single-dose, parallel design study.

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72h}$ 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%.