Notes on the Design of Bioequivalence Study:

Pretomanid

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. 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 products containing pretomanid.

Pharmacokinetics of pretomanid

Administration of 200 mg pretomanid with a high-fat, high-calorie meal increased mean C_{max} by 76% and mean $AUC_{0\text{-}inf}$ by 88% as compared with administration in the fasted state. The median t_{max} values range from 4 to 5 hours. Pretomanid has a half-life of 17 hours (14 – 26 h). In the fasted state, bioavailability decreased with increasing doses (50 to 1500 mg/day), with absorption saturation above 1000 mg. In the fed state, there were no significant changes in bioavailability across doses of 50 mg through 200 mg. Pretomanid should be taken with food.

Guidance for the design of bioequivalence studies

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

Study design: A single-dose crossover design is recommended.

Dose: As the EoI includes pretomanid tablet 200 mg only, the bioequivalence study should be conducted with this strength.

Fasted/fed: As the comparator product should be taken with food, a fed state study is recommended. Pretomanid tablets should be administered either with a high-fat, high-calorie meal or with a low-fat, low-calorie meal.

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. Therefore, bioequivalence should be based on the determination of pretomanid.

Sample size: The intra-subject variability of C_{max} and $AUC_{0\text{-}t}$ of pretomanid in the fed state has been reported to be 11.2% and 4.8%, respectively, in the literature (Zou Y et al. Characterizing Absorption Properties of Dispersible

Pretomanid Tablets Using Population Pharmacokinetic Modelling. Clin Pharmacokinet. 2022; 61(11):1585-1593. doi: 10.1007/s40262-022-01163-w.). This data may facilitate the calculation of a sufficient sample size for a single-dose crossover bioequivalence study.

Washout: Taking into account an elimination half-life for pretomanid of 14 – 26 h, a washout period of seven days is considered sufficient to prevent carry over.

Blood sampling: The blood sampling should be intensive between three and five and half hours after administration to properly characterize the C_{max} of pretomanid. For example, samples can be taken pre-dose and 0.50,1.00, 1.50, 2.00, 2.50, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 4.75, 5.00, 5.25, 5.50, 6.00, 9.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after drug administration.

Analytical considerations: Information currently available indicates that it is possible to measure pretomanid in human plasma using LC-MS/MS analytical methodology. 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 pretomanid should meet the following bioequivalence standards in the single-dose crossover design study(ies):

- 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%.