Notes on the design of bioequivalence study: Rifabutin

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 immediate release products containing rifabutin.

Pharmacokinetics of rifabutin

Rifabutin maximum plasma concentrations are reached approximately 2-4 hours after oral administration. The pharmacokinetics of rifabutin are linear after single administration of 300, 450, and 600 mg to healthy volunteers. With these doses, Cmax is in the range of 0.4-0.7 µg/ml. The half-life of rifabutin is approximately 35-40 hours. Rifabutin can be administered independently of meals.

Guidance for the design of bioequivalence studies:

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

Design: A single-dose crossover design is recommended.

Dose: As the EoI includes only the 150 mg tablet or capsule, the 150 mg strength is recommended for the bioequivalence study. A dose of 1x150 mg should be tested.

Fasted/fed: The bioequivalence study should be conducted in the fasted state because rifabutin can be administered independent of meals.

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 for rifabutin.

Sample size: Rifabutin pharmacokinetic parameters, C_{max} and AUC_{0-t}, in the fasting state seem to display high intra-subject variability (36% for AUC), based on Moyle et al. *Br J Clin Pharmacol.* 54(2): 178–182. However, as there is only limited data available, a pilot study is recommended to estimate the intra-subject variability of AUC_{0-t} and C_{max}.

Washout: Taking into account the elimination half-life of rifabutin of 40 h, a wash-out period of at least 14 days is considered sufficient to prevent carry-over.

Blood sampling: Samples should be taken at pre-dose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, and 72.0 h after drug administration. Considering the elimination half-life, it is sufficient to take blood samples up to 72 hours after administration for the characterization of rifabutin pharmacokinetics.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure rifabutin 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).

Statistical considerations: The data for rifabutin should meet the following bioequivalence standards in a single-dose cross-over design study:

The 90% confidence interval of the relative mean AUC_{0-72h} of the test to reference product should be within 80.00–125.00%

- The 90% confidence interval of the relative mean C_{max} of the test to reference product should be within 80.00–125.00%.

Information currently available to PQT/MED indicates that the comparator product is a highly variable drug product. Therefore, if the Applicant suspects that the variability of C_{max} or AUC_{0-72h} is high (CV>30%), the applicant may prefer to employ a full replicate design study in order to widen the acceptance range of C_{max}. and/or AUC_{0-t}. For more information on replicate study designs and widening the limits of average bioequivalence, refer to Section 7.9.3 of Annex 8, TRS 1052 and WHO guidance document “Application of reference-scaled criteria for AUC in bioequivalence studies conducted for submission to PQT/MED”.