Notes on the design of bioequivalence study: Rifapentine

Notes on the design of bioequivalence studies with products invited to be submitted 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: *Fisty-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 rifapentine.

Pharmacokinetics of rifapentine

Maximum concentrations were observed from 4 to 6 hours after administration of a 150-600 mg rifapentine dose.

The administration of rifapentine with a high fat meal (850 total calories: 33 g protein, 55 g fat and 58 g carbohydrate) increased $AUC_{0-\infty}$ and Cmax by 43% and 44%, respectively, over that observed when administered under fasted conditions. The administration of rifapentine (900 mg single dose), concomitant with a low fat, high carbohydrate breakfast, led to an increase of rifapentine bioavailability by 47% in Cmax and 51% in AUC.

Rifapentine half-life is approximately 15 hours (13.2 – 14.1 hours) and it was similar across the 150-600 mg dose range.

Guidance for the design of bioequivalence studies:

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

Design: A cross-over design is recommended.

Dose: The EoI includes the 300 mg tablets (scored) and 150 mg tablets (scored and dispersible). As these products will differ in formulation and posology, these products will be considered separately, and a bioequivalence study will be required for each development. For the 300 mg tablets a dose of 1 x 300 mg of the test product vs. 2 x 150 mg of the reference product should be tested.

When conducting bioequivalence studies, it is essential to administer the test and the comparator product according to their corresponding instructions for use. In those cases where the test and the comparator product are different dosage forms with different methods of administration (e.g., a tablet that should be taken with a glass of water vs. a dispersible tablet to be dispersed in 10 mL of water) the bioequivalence study should be conducted employing the intended method of administration of each product. It is considered incorrect to standardise the volume of liquid in all these cases (e.g. administering a glass of water after the intake of a dispersible tablet or rinsing the container where a dispersible tablet has been suspended with the remaining liquid of a glass of water) because this standardisation does not occur in real life conditions. The total volume of water employed during administration of a pediatric dispersible tablet should not exceed 50 mL.

Fasting/fed: The bioequivalence study should be conducted in the fed state as food increases the bioavailability of rifapentine. As a low-fat high-carbohydrate breakfast increases Cmax and AUC as much as or more than the high-fat high-calorie breakfast, a standard breakfast (non-high-fat breakfast, 550 Kcal) is recommended since it is more similar to the meal composition of patients. However, a high-fat high-calorie breakfast is also acceptable in those cases where the fed study is to be submitted also to other regulatory agencies where bioequivalence demonstration is required both in the fasting and the fed state. In such cases, both studies (in fasting and fed state) should be submitted.

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 rifapentine.

Sample size: Rifapentine pharmacokinetic parameters, Cmax and AUC_{0-t}, in the fed state seem to possess low to moderate variability (10–20%), based on information available to the PQTm. These data will facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: Taking into account the half-life of 15 h, a wash-out period of at least 7 days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive between 3 and 6 hours after administration. For example, samples should be taken at predose, 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 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.

Analytical considerations: Information currently available indicates that it is possible to measure rifapentine 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 rifapentine should meet the following bioequivalence standards in a single-dose cross-over design study:

- The 90% confidence interval of the relative mean AUC_{0-t} of the test to reference product should be within 80-125%
- The 90% confidence interval of the relative mean C_{max} of the test to reference product should be within 80-125%.