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 Team – Medicines (PQTm) 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.


Below, additional specific guidance is provided on the invited immediate release products containing rifapentine.

Pharmacokinetics of rifapentine

The absolute bioavailability of rifapentine has not been reported. The relative bioavailability (with an oral solution as a reference) of rifapentine after a single 600 mg dose to healthy adult volunteers was 70%. Following a single 600 mg oral dose of radiolabeled rifapentine to healthy volunteers (n=4), 87% of the total 14C-rifapentine was recovered in the urine (17%) and feces (70%). Greater than 80% of the total 14C-rifapentine dose was excreted from the body within 7 days.

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 fasting 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. The changes in rifapentine Cmax and AUC$_{0-\infty}$ were dose linear, but disproportionate (more than proportional) from 150 to 600 mg. Two-fold increases in dose from 150 to 300 mg and from 300 to 600 mg resulted in 3.2- fold and 2.2-fold increases in AUC$_{0-\infty}$, respectively. Over the entire dose range studied, a 4-fold increase in dose resulted in a 7.2-fold increase in AUC$_{0-\infty}$. The dose-disproportionate increases in Cmax with single, increasing doses of rifapentine were less pronounced. A 4-fold increase in dose from 150 to 600 mg resulted in a 5.2-fold increase in Cmax (Keung et al. Single and multiple dose pharmacokinetics of rifapentine in man: part II. Int J Tuberc Lung Dis. 1999 May;3(5):437-44.).

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:** As the EoI includes the 300 mg and 150 mg tablets, the highest strength of 300 mg is recommended for the single dose bioequivalence study due to the more than proportional increase of AUC of rifapentine with increasing doses. A dose of 1 x 300 mg of the test product vs. 2 x 150 mg of the reference product should be tested.
**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 volunteers

**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:** At least 7 days.

**Blood sampling:** Predose, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 24, 36, 48, and 72 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\(_{\text{max}}\) in most profiles of each formulation (test or comparator).

**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.

**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\(_{\text{max}}\) of the test to reference product should be within 80-125%.