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. In particular, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: *Fifty-first report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations,* Geneva, World Health Organization, 2017. WHO Technical Report Series, No. 1003, Annex 6.

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 C_{max} 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 C_{max} and 51% in AUC.

Rifapentine half-life is approximately 15 hours (13.2 – 14.1 hours) and similar across the 150-600 mg dose range. The changes in rifapentine C_{max} 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 C_{max} 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 C_{max} (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 single-dose cross-over design is recommended.

Dose: As the EoI includes the 300 mg and 150 mg tablets, the higher strength (i. e. 300 mg) is recommended for the single dose bioequivalence study in view of the more than proportional increase in rifapentine AUC with dose. A dose of 1 x 300 mg of the test product *vs.* 2 x 150 mg of the reference product should be tested.

Fasted/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 C_{max} 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 fasted and the fed state. In such cases, both studies (in fasted and fed state) should be submitted.

Subjects: Healthy adults 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.

Sample size: Rifapentine pharmacokinetic parameters, C_{max} and AUC_{0-t}, in the fed state seem to possess low to moderate variability (10–20%), based on information available to the PQT/MED. 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 80.00 – 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%.