Notes on the design of bioequivalence study: Bedaquiline

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-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 bedaquiline.

Pharmacokinetics of Bedaquiline

Bedaquiline is absorbed slowly after oral administration with a median T_{max} of 4 to 6 hours. C_{max} and the area under the plasma concentration-time curve (AUC) increased proportionally up to the highest doses studied (700 mg single-dose and once daily 400 mg multiple doses).. In several studies a second peak was observed in the plasma concentration-time profile either due to bile salts aiding solubility and thereby absorption, or due to enterohepatic recycling. The intake of a normal breakfast (not a high-fat, high-calorie breakfast) increases bedaquiline absorption (2.6-fold increase in C_{max} and 1.9-fold increase in AUC in one study, and 3.8-fold for C_{max} and 2.4-fold for AUC in another study with the same type of breakfast). The food effect from an oral solution was less pronounced (AUC increased only 27%) probably because the oral solution contained solubility enhancers or because of the intake of a different type of breakfast. The effect of high-fat meal has not been investigated. Bedaquiline is intended to be taken with food.

Bedaquiline is reported to exhibit a long terminal elimination half-life of approximately 5.5 months in patients, but approximately 30 hours in healthy volunteers after a 400 mg single-dose. The effective half-life is much shorter based on the accumulation ratio at 14 days (effective half-life of 24 h) and also the time to steady state (effective half-life of *ca.* 2 days).

No inter-conversion of bedaquiline into either the RR or the SS enantiomer was observed *in vivo*.

Guidance for the design of bioequivalence studies:

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

Design: A single-dose cross-over design is recommended.

Dose: The EoI includes a 100 mg tablet for adults and a 20 mg scored and dispersible tablet for children. For a 100 mg tablet for adults, the proposed product should be compared to 1 x 100 mg of the comparator tablet, while for a 20 mg scored and dispersible tablet for children, it is recommended that the proposed product be compared to 1 x 20 mg of the dispersible comparator product.

When conducting bioequivalence studies, it is essential to administer the test and the comparator product according to their corresponding instructions for use. 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.

Fasted/fed: The bioequivalence study should be conducted in the fed state with a normal breakfast (500 – 600 Kcal), not a high-fat, high-calorie meal. For the adult tablets, the products should be administered as intact tablets following consumption of the meal. For pediatric dispersible tablets, the products should be administered using one of the following approaches after consumption of the meal: 1. dispersed in water and administered; 2. dispersed in water, further mixed with a beverage or soft food, and administered; or 3. Crushed, mixed with soft food, and administered.

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 of bedaquiline.

Sample size: Information currently available to PQT/MED suggests that the intra-subject variability is 15% in fed state and 25 – 34% in fasted state. These data may facilitate the calculation of a sufficient sample size for the single-dose cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of the bedaquiline in healthy volunteers is reported to be approximately 30 hours, a cross-over design with a wash out period of at least 4 weeks could be feasible. Plasma levels may be detected at pre-dose samples after 4 weeks, but those are expected to be less than 5% of C_{max}.

Blood sampling: The blood sampling should be intensive between 4 and 6 hours after administration to characterise C_{max} adequately. It is not necessary to take samples after 72 hours. For example, blood samples might be taken at pre-dose, 1.00, 2.00, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 h after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure bedaquiline in human plasma using LC-MS/MS analytical methodology with a LLOQ of 1 ng/ml. 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 bedaquiline should meet the following bioequivalence standards in a single-dose parallel or cross-over design study:

- The 90% confidence interval of the relative mean $AUC_{0\text{-}72h}$ 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%.