# Notes on the Design of Bioequivalence Study: Tafenoquine

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team – Medicines (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 tafenoquine.

## Pharmacokinetics of tafenoquine

Following single dose administration of 200 mg of tafenoquine (as two 100-mg tablets) in healthy adult subjects under fed conditions with a high-calorie, high-fat meal (approximately 1000 calories with 19% protein, 31% carbohydrate, and 50% fat), the maximum concentration was reached 14 h (6 - 72 h) after drug administration. Following administration of a single dose of tafenoquine orally under fasted conditions in healthy adult subjects, AUC and Cmax increased dose proportionally over the dose range from 100 mg to 400 mg. The mean terminal half-life of tafenoquine is approximately 16.5 days (range: 10.8 days to 27.3 days) in healthy adult subjects.

## Guidance for the design of bioequivalence studies

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

**Study design:** A single-dose parallel design is recommended.

**Dose:** As the EoI includes tafenoquine 150 mg tablet and 50 mg dispersible tablet, the bioequivalence study should be conducted with these products and strengths.

**Fasted/fed:** The bioequivalence study should be conducted in the fed state as tafenoquine is recommended to be taken with food.

**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 the parent compound.

**Sample size:** Information currently available indicates that the inter-subject variability of $C_{max}$ and $AUC_{0\text{-}72h}$ of tafenoquine was around 21% (Goyal N et al. Application of the Stable Isotope Label Approach in Clinical

Development-Supporting Dissolution Specifications for a Commercial Tablet Product with Tafenoquine, a Long Half-life Compound. AAPS J. 2018; 20(4):74. doi: 10.1208/s12248-018-0234-5 and TGA, AusPAR Attachment 2. https://www.tga.gov.au/sites/default/files/auspar-tafenoquine-succinate-190408-cer.pdf). These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

**Washout:** N/A

**Blood sampling:** The blood sampling should be moderately intensive for the whole duration of the sampling, since $T_{max}$ has exhibited a wide dispersion, to properly characterize the $C_{max}$ of tafenoquine. Blood samples for the characterization of tafenoquine pharmacokinetics should be taken for 72 h post-dose in order to determine $AUC_{0-72h}$. For example, blood samples might be taken at pre-dose, 2.00, 4.00, 6.00, 8.00, 10.00, 12.00, 14.00, 16.00, 18.00, 20.00, 24.00, 28.00, 32.00, 36.00, 40.00, 48.00, 56.00, 64.00 and 72.00 h after drug administration.

**Analytical considerations:** Information currently available to PQT/MED indicates that it is possible to measure tafenoquine 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 tafenoquine should meet the following bioequivalence standards in a single-dose parallel design study:

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