

Notes on the Design of Bioequivalence Study: Fexinidazole

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.

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 fexinidazole.

Pharmacokinetics of fexinidazole

Following oral administration of a single 1200 mg dose to fasted, healthy, adult male volunteers, fexinidazole was rapidly absorbed and extensively metabolised with exposures (C_{max}/AUC_{0-24h}) of metabolites which were 6.76/8.67 (M1) and 6.27/10.4 (M2) - fold higher than that of fexinidazole. Food intake markedly increased the bioavailability of fexinidazole, and subsequent both metabolites, by 2.4 to 3.0-fold. Following oral administration to healthy fed volunteers at the recommended treatment regimen for fexinidazole (1800 mg once daily for four days and then 1200 mg once daily for six days), median peak plasma concentrations were at 4 hours for fexinidazole and M1, and at 24 hours for M2 after the first dose. Steady state was reached between 7 and 10 days for all analytes. The tablets should be taken with food.

In healthy subjects, following the full 10-day treatment regimen, the mean plasma terminal half-life for fexinidazole was 14 hours.

In healthy male volunteers, following single oral dosing of fexinidazole over the range 100 to 3600 mg, under fasted conditions, the systemic exposure of fexinidazole (and subsequently to M1 and M2) was generally less than dose-proportional.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of fexinidazole 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 fexinidazole 600 mg tablet only, the bioequivalence study should be conducted with this strength.

Fasting/fed: As fexinidazole tablets should be taken with food, a fed state study is recommended. It is recommended that the meal employed in the study be a standard meal, representative of the meals of the patient population. The meal composition does not need to be a high-fat high-calorie meal.

Subjects: Healthy adult subjects should be utilized. It is not necessary to include patients in the bioequivalence study.

Sample size: Fexinidazole C_{max} seems to be highly variable (31.8% approx.). These data may facilitate the calculation of a sufficient sample size for a cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of fexinidazole in healthy volunteers of 14 hours, a washout period of seven days is considered sufficient to prevent carry over.

Blood sampling: The blood sampling should be intensive for the first four hours after administration to properly characterize the C_{max} of fexinidazole. It is not necessary to take blood samples beyond 60 hours for the characterization of fexinidazole pharmacokinetics. For example, samples can be taken pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 3.75, 4.00, 4.25, 4.50, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 60 hours.

Analytical considerations: Information currently available indicates that it is possible to measure fexinidazole 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).

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. The disposition of fexinidazole should be characterized and the determination of bioequivalence will be based on the parent compound.

Statistical considerations: The data for fexinidazole should meet the following bioequivalence standards in a single-dose, crossover 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%.

Information currently available to the PQTm suggests that the comparator product might be a highly variable drug product for C_{max} , but not for AUC_{0-t} . Widening of the acceptance range for C_{max} might be acceptable if the applicant conducts a replicate cross-over study to estimate variability of the comparator product more accurately and the high variability of C_{max} is demonstrated. For more information on replicate study designs and scaled average bioequivalence refer to Section 7.9.3 of Annex 6, TRS 1003.