Notes on the Design of Bioequivalence Study: Nifedipine

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. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in: *Fifty-seventh Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

Below, additional specific guidance is provided on the invited immediate release dosage forms containing nifedipine.

Pharmacokinetics of nifedipine

After oral administration nifedipine is immediately and almost completely absorbed. The systemic availability of orally administered nifedipine is 45 - 56% owing to a first pass effect. Maximum plasma and serum concentrations are reached at 30 to 60 minutes. Simultaneous food intake leads to delayed, but not reduced absorption. The terminal elimination half-life is 1.7 to 6 hours.

Guidance for the design of bioequivalence studies

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

Design: A single-dose, crossover design is recommended.

Dose: As the EoI includes 10 and 20 mg tablets, the highest strength should be tested. The additional strength of 10 mg can be waived if the conditions for the additional strength biowaiver are met. As the reference product is marketed at the 10 mg strength 1 unit of 20 mg of the test product should be compared to 2 units of 10 mg of the comparator product.

Fasted/fed: As the comparator product can be taken with or without food, a fasted state study is recommended.

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 nifedipine.

Sample size: Information currently available to the PQT/MED indicates that the intra-subject variability for nifedipine C_{max} is around 45% and 17% for AUC. These data will facilitate the calculation of sufficient sample size for the cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of nifedipine of up to 6 hours, a washout period of one week is considered sufficient to prevent carry over.

Blood sampling: As nifedipine median t_{max} can range between 0.5 h and 1.0 h, blood sampling should be intensive the first hour after administration to cover the peak of nifedipine, e.g., pre-dose and at 0.17, 0,33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 4.50, 6.00, 8.00, 12.00, 16.00 and 24.00 hours post dose.

Analytical method: Information currently available to the PQT/MED indicates that it is possible to measure nifedipine in human plasma using LC-MS/MS analytical methodology (LLOQ of 0.5 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). See Guideline on bioanalytical method validation and study sample analysis. In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised Guideline M10 for more information on bioanalytical recommendations.

Statistical considerations: The data for nifedipine 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_{max} of the test to reference product should be within 80-125%.