Notes on the Design of Bioequivalence Study:
Gatifloxacin

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 gatifloxacin.

Pharmacokinetics of gatifloxacin

Gatifloxacin is well absorbed from the gastrointestinal tract after oral administration and can be given without regard to food. The absolute bioavailability of gatifloxacin is 96%. Peak plasma concentrations of gatifloxacin usually occur 1-2 hours after oral dosing. Gatifloxacin pharmacokinetics are linear and time-independent at doses ranging from 200 to 800 mg administered over a period of up to 14 days. The mean elimination half-life of gatifloxacin ranges from 7 to 14 hours.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of gatifloxacin, 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 Gatifloxacin tablets of 200 mg and 400 mg (scored), the bioequivalence study should be conducted with the highest strength.

Fasted/fed: The bioequivalence study should be conducted in the fasting state.

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 gatifloxacin.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability for gatifloxacin is around 27%. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: Taking into account the elimination half-life of gatifloxacin of 7 – 14 h, a washout period of 7 days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive for the first two – three hours after administration to properly characterize the C_{max} of gatifloxacin. For example, blood samples should be taken at pre-dose, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00 and 48.00 h after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure gatifloxacin in human plasma using LC-MS/MS analytical methodology with a LLOQ of 10 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 gatifloxacin 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%.