Notes on the Design of Bioequivalence Study: Azithromycin

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 Azithromycin.

Pharmacokinetics of Azithromycin

Peak plasma concentrations are attained 2 to 3 hours after taking the medicinal product. The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days. The comparator tablets should be taken irrespective of meals in the USA.

Guidance for the design of bioequivalence studies

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

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

Dose: As the EoI includes Azithromycin 500 mg tablet, the bioequivalence study should be conducted with this product.

Fasted/fed: The bioequivalence study should be conducted in the fasted state as azithromycin tablet can be taken irrespective of meals.

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 azithromycin.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability for azithromycin is around 33%. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: Taking into account the elimination half-life of azithromycin of 2-4 days, a washout period of 21 days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive for the first hours after administration to properly characterize the C_{max} of Azithromycin. Blood samples for the characterization of Azithromycin pharmacokinetics should be taken for 72 h post-dose in order to determine AUC_{0-t}. For example, blood samples might be taken at pre-dose, 0.5, 1.0, 1.5, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 48.0, 72.0 after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure azithromycin 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 azithromycin 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 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%.