Notes on the Design of Bioequivalence Study:
Lamivudine/Abacavir

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.


Below, additional specific guidance is provided on the invited immediate release products containing lamivudine and abacavir.

Pharmacokinetics of lamivudine and abacavir

Maximum lamivudine concentrations are observed in plasma within 0.5 to 3.0 hours of dosing in the fasted state (median Tmax of 1 - 1.5 hour). The half-life of lamivudine is 5-7 hours. Co-administration of lamivudine with food results in a delay of Tmax and a lower Cmax (decreased by 47%). However, the extent (based on the AUC) of lamivudine absorption is not influenced. Therefore, lamivudine can be taken with or without food.

Maximum abacavir concentrations are observed in plasma within 0.5 to 3.0 hours of dosing in the fasted state (median Tmax of 1 - 1.5 hour). The half-life of abacavir is 1.5 hours. Food delayed absorption and decreased Cmax of abacavir but did not affect overall plasma concentrations (AUC). Therefore, abacavir can be taken with or without food.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of lamivudine and abacavir 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 lamivudine/abacavir 300/600 mg tablet (preferably scored) and 60/120mg tablet (scored and dispersible), the bioequivalence study should be conducted with the 300/600 mg tablet if both strengths are developed and the conditions for an additional strength biowaiver are fulfilled. Otherwise, a bioequivalence study is required for each proposed product. As lamivudine and abacavir are BCS Class III APIs, a BCS-based biowaiver for a proposed 300/600mg product may be possible if the requirements for such a biowaiver are met.
When conducting bioequivalence studies, it is essential to administer the test and the comparator product according to their corresponding instructions for use. In those cases where the test and the comparator product are different dosage forms with different methods of administration (e.g. a tablet that should be taken with a glass of water vs. a dispersible tablet to be dispersed in 10 mL of water) the bioequivalence study should be conducted employing the intended method of administration of each product. It is considered incorrect to standardise the volume of liquid in all these cases (e.g. administering a glass of water after the intake of a dispersible tablet or rinsing the container where a dispersible tablet has been suspended with the remaining liquid of a glass of water) because this standardisation does not occur in real life conditions.

**Fasting/fed:** As lamivudine and abacavir can be taken with or without food, a fasted state study is recommended.

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

**Sample size:** Lamivudine \( C_{\text{max}} \) and abacavir \( C_{\text{max}} \) seems to be moderately variable (15 - 25% 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 lamivudine in healthy volunteers of 5-7 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 \( C_{\text{max}} \) of lamivudine and abacavir. It is not necessary to take blood samples beyond 24 hours for the characterization of lamivudine pharmacokinetics and 12 hours for abacavir. For example, samples can be taken pre-dose and at 0.16, 0.33, 0.50, 0.67, 0.83, 1.00, 1.16, 1.33, 1.50, 1.75, 2.00, 2.16, 1.33, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00 and 12.00, 16.00 and 24.00 hours.

**Analytical considerations:** Information currently available indicates that it is possible to measure lamivudine and abacavir in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of the \( C_{\text{max}} \) in most profiles of each formulation (test or comparator).

**Parent or metabolite data for assessment of bioequivalence:** The parent drugs are considered to best reflect the biopharmaceutical quality of the product. The disposition of lamivudine and abacavir should be characterized and the determination of bioequivalence will be based on the parent compounds.

**Statistical considerations:** The data for lamivudine and abacavir should meet the following bioequivalence standards in a single-dose, crossover design study:

- The 90% confidence interval of the relative mean \( \text{AUC}_{0-t} \) of the test to reference product should be within 80–125%

- The 90% confidence interval of the relative mean \( C_{\text{max}} \) of the test to reference product should be within 80–125%.