Notes on the design of bioequivalence study: Dolutegravir

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 Dolutegravir.

**Pharmacokinetics of Dolutegravir**

Dolutegravir is rapidly absorbed following oral administration, with a median Tmax at 2 to 3 hours post-dose for the conventional-release tablet formulation. Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir AUC\(_{0-\infty}\) by 33%, 41%, and 66%, increased Cmax by 46%, 52%, and 67%, prolonged Tmax to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases may be clinically relevant in the presence of certain integrase class resistance. Therefore, dolutegravir is recommended to be taken with food by patients infected with HIV with integrase class resistance. Otherwise, dolutegravir can be taken with or without food.

Dolutegravir has a terminal half-life of approximately 14 hours approximately.

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of conventional-release tablet formulations, dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure at doses greater than 50 mg.

**Guidance for the design of bioequivalence studies:**

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

**Dose:** The EoI includes 50 mg conventional-release tablets of dolutegravir for adults and adolescents as well as 5 and 10 mg dispersible tablets for children.

With respect to the conventional-release tablets, applicants developing a 50 mg conventional-release product should use the 50 mg comparator product in the bioequivalence comparison.
At this time, an appropriate comparator product for the 5 and 10 mg dispersible tablet products is not available. There is literature demonstrating that the dolutegravir dispersible product currently under development by the manufacturer of Tivicay, the comparator product, is not bioequivalent to the conventional-release comparator tablet product. Therefore, the conventional-release comparator tablet cannot be used for the development of a generic dispersible tablet product. Once the 5 mg dispersible tablet of the comparator becomes available, bioequivalence between proposed 5 and 10 mg dispersible tablets and the 5 mg dispersible tablet of the comparator should be demonstrated. If an additional strength biowaiver is to be requested, bioequivalence should be demonstrated with the highest strength proposed dispersible tablet (i.e. 10 mg) versus 2 tablets of the 5 mg dispersible tablet of the comparator product. An additional strength biowaiver could be submitted for the lower strength (i.e. 5 mg dispersible tablet) if the requirements for the additional strength biowaiver are met.

**Fasting/fed:** The bioequivalence studies should be conducted in the fasting state as dolutegravir is recommended to be taken with or without food.

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

**Power:** Information on dolutegravir currently available to the PQTm indicates that the intra-subject variability for Dolutegravir is around 20%. These data will facilitate the calculation of sufficient power for the bioequivalence studies.

**Washout:** Taking into account the elimination half-life of dolutegravir in healthy volunteers (approximately fourteen hours), a washout period of seven days is considered sufficient to prevent carry over.

**Blood sampling:** The blood sampling for dolutegravir should be intensive the first three hours after administration to properly characterize the C\text{max} of dolutegravir. It is not necessary to take blood samples beyond 72 hours.

**Analytical considerations:** Information currently available to the PQTm indicates that it is possible to measure dolutegravir 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 drug is considered to best reflect the biopharmaceutical quality of the product. The data for the parent compound should be used to assess bioequivalence.

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

- The 90% confidence interval of the relative mean AUC\text{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%.

Information currently available to the PQTm indicates that the comparator product is not a highly variable drug product.