Notes on the Design of Bioequivalence Study: Dolutegravir

Notes on the design of bioequivalence studies with products invited for submission 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 may 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 median $T_{\text{max}}$ at 2 to 3 hours post-dose for tablet formulation.

Food increases the extent and slowed the rate of absorption of dolutegravir. The bioavailability of dolutegravir depends on meal content: low-, moderate-, and high-fat meals increased dolutegravir AUC(0-$\infty$) by 33%, 41%, and 66%, increased $C_{\text{max}}$ by 46%, 52%, and 67%, prolonged $T_{\text{max}}$ 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.

The linearity of dolutegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, in general, dolutegravir exhibited nonlinear pharmacokinetics with less than dose-proportional increases in plasma exposure from 2 mg to 100 mg; however increase in dolutegravir exposure appears to be dose proportional from 25 mg to 50 mg for the tablet formulation. With 50 mg twice daily, the exposure over 24 hours was approximately doubled compared to 50 mg once daily.

**Guidance for the design of bioequivalence studies**

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

**Dose:** A single oral dose of one tablet of dolutegravir 50 mg should be feasible. The bioanalytical method should be sufficiently sensitive to detect concentrations that are 5% of $C_{\text{max}}$ in most profiles of each formulation (test or comparator).
**Fasting/fed:** The bioequivalence study should be conducted in the fasting state as dolutegravir is recommended to be taken with or without food.

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

**Sample size:** Information on dolutegravir currently available to PQTm indicates that the intra-subject variability for dolutegravir is approximately 15–25%. These data will facilitate the calculation of the sample size for the bioequivalence study.

**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 for 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 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 $\text{AUC}_{T}$ 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 PQTm indicates that the comparator product is not a highly variable drug product.