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 (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 dolutegravir.

Pharmacokinetics of dolutegravir

Dolutegravir is rapidly absorbed following oral administration, with a median T_{max} at 2 to 3 hours post-dose for the conventional-release tablet formulation and at 0.75 to 1.5 h post-dose for the dispersible tablet. 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 $AUC_{0\text{-}inf}$ by 33%, 41%, and 66%, increased C_{max} by 46%, 52%, and 67%, prolonged T_{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 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:

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

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

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

As the dolutegravir dispersible comparator tablet is not bioequivalent to the conventional-release comparator tablet, bioequivalence should be demonstrated between the proposed 5 and 10 mg dispersible tablets and the 5 mg comparator dispersible tablet. If an additional strength biowaiver is applied, bioequivalence should be demonstrated with the highest strength of the applied dispersible tablet (*i.e.* 10 mg) *versus* 2 tablets of the 5 mg comparator

dispersible tablet. The additional strength biowaiver could be submitted for the low strength (*i.e.* 5 mg dispersible tablet) if the requirements for the additional strength 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. 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.

Fasted/fed: The bioequivalence studies should be conducted in the fasted 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.

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.

Sample size: Information on dolutegravir currently available to PQT/MED indicates that the intra-subject variability for Dolutegravir is around 20%. These data may facilitate the calculation of sufficient sample size for a single-dose cross-over bioequivalence study.

Washout: Taking into account the elimination half-life of dolutegravir in healthy volunteers (approximately 14 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_{max} of dolutegravir. It is not necessary to take blood samples beyond 72 hours.

Analytical considerations: Information currently available to PQT/MED 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_{max} in most profiles of each formulation (test or comparator).

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_{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%.