Notes on the Design of Bioequivalence Study:
Darunavir

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 can be considered acceptable if justified by sound scientific evidence.


Below, additional specific guidance is provided on the invited immediate release products containing darunavir.

Pharmacokinetics of darunavir

Darunavir, co-administered with 100 mg ritonavir twice daily, is absorbed following oral administration with a $T_{\text{max}}$ of approximately 2.5–4 hours. The absolute oral bioavailability of a single 600 mg dose of darunavir alone and after coadministration with 100 mg ritonavir twice daily is 37% and 82%, respectively.

When administered with food, the $C_{\text{max}}$ and AUC of darunavir, co-administered with ritonavir, is approximately 30% higher relative to the fasting state. Therefore, darunavir, co-administered with ritonavir, should always be taken with food. Within the range of meals studied, darunavir exposure is similar. The total caloric content of the various meals evaluated ranged from 240 Kcal (12 g fat) to 928 Kcal (56 g fat).

The terminal elimination half-life of darunavir is approximately 15 hours when co-administered with ritonavir. After intravenous administration, the clearance of darunavir, administered alone and co-administered with 100 mg twice-daily ritonavir, is 32.8 L/h and 5.9 L/h, respectively.

In adults, linear pharmacokinetics are observed after single dose administration over the 300–1200 mg darunavir dose range with 100 mg ritonavir.

Guidance for the design of bioequivalence studies

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

**Dose:** Due to the linear / dose-proportional pharmacokinetics of darunavir and its low solubility, the maximum strength in the application to PQ (i.e. 800 mg for the 400 mg, 600 mg and 800 mg strengths) should be employed in the bioequivalence study. The study can be conducted with or without concomitant administration of ritonavir. If the study is carried out with concomitant ritonavir administration, the ritonavir dosing should be started at least two days before administration of darunavir and maintained until the end of pharmacokinetic sampling of each treatment. A single oral dose of each formulation (test or comparator) in each study period should be employed.
**Fasting/fed:** The bioequivalence study should be conducted in the fed state as darunavir is recommended to be taken with food because of the increased bioavailability, irrespective of the total caloric contents of the meal. Therefore, we recommend administration with a standard breakfast, not a high-fat, high-calorie meal, as a standard breakfast is considered to be closest to real-life conditions in patients.

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

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

**Washout:** Taking into account the elimination half-life of darunavir in healthy volunteers (about 15 hrs), a washout period of seven days is considered sufficient to prevent carry over.

**Blood sampling:** The blood sampling for darunavir should be intensive the first four hours after administration to cover the rate and extend of absorption of darunavir. It is not necessary to take blood samples beyond 72 hours, as this will only substantiate the elimination phase darunavir.

**Analytical considerations:** Information currently available to the PQ indicates that it is possible to measure darunavir in human plasma using LC-MS/MS analytical methodology. The bioanalytical method should be validated in the presence of ritonavir if the study is conducted with concomitant administration of ritonavir.

**Parent or metabolite data for assessment of bioequivalence:** The parent drug is considered to best reflect the rate and extent of absorption for darunavir. The data for the parent compound will be used to assess bioequivalence.

**Statistical considerations:** The data for darunavir 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 \( \text{C}_{\text{max}} \) 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. However, if the applicant suspects that the variability of \( \text{C}_{\text{max}} \) is high (CV > 30%), the applicant may prefer to design a replicate design study for at least the comparator product in order to scale the acceptance range of \( \text{C}_{\text{max}} \) only. Refer to Section 7.9.3 of Annex 7, TRS 992 for more information.