Notes on the Design of Bioequivalence Study: Valganciclovir

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Unit – Medicines Assessment Team (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-seventh report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva, World Health Organization, 2024. WHO Technical Report Series, No. 1052, Annex 8.

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

Pharmacokinetics of valganciclovir

Valganciclovir is a prodrug of ganciclovir. It is well absorbed from the gastrointestinal tract and rapidly and extensively metabolised in the intestinal wall and liver to ganciclovir. Its maximum concentrations are observed between 1 and 2 h after administration in fed state. Systemic exposure to valganciclovir is transient and low with a half-life of 0.9 h.

When valganciclovir was given with food at the recommended dose of 900 mg, higher values were seen in both mean ganciclovir AUC (approximately 30 %) and mean ganciclovir C_{max} values (approximately 14 %) than in the fasting state. Valganciclovir tablets should be taken with food whenever possible.

Guidance for the design of bioequivalence studies

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

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

Dose: As the EoI includes valganciclovir tablets of 450 mg, the bioequivalence study should be conducted with this strength.

Fasted/fed: The bioequivalence study should be conducted in fed state.

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

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 of valganciclovir.

Sample size: Information currently available to PQT/MED indicates that the intra-subject variability for valganciclovir is around 22.5%. These data may facilitate the calculation of a sufficient sample size for the bioequivalence study.

Washout: Taking into account the elimination half-life of valganciclovir of 0.9 h, a washout period of 7 days is considered sufficient to prevent carry-over.

Blood sampling: The blood sampling should be intensive for the first two hours after administration to properly characterize the C_{max} of valganciclovir. For example, blood samples should be taken at pre-dose, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00 and 10.00 h after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure valganciclovir in human plasma using LC-MS/MS analytical methodology with a LLOQ of 1 ng/ml. 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 valganciclovir should meet the following bioequivalence standards in a single-dose cross-over 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%.

Biowaiver: A BCS-based biowaiver for valganciclovir is considered a possible alternative to a bioequivalence study, provided the requirements for granting a BCS-based biowaiver are met as outlined in the WHO Guideline "Biopharmaceutics Classification System-Based Biowaivers" (TRS 1052, Annex 7, 2024) and the PQT/MED guidance "PQT/MED-specific Annotations for the WHO Guideline for Biopharmaceutics Classification System (BCS)-based Biowaiver Applications" (2024).