

Notes on the Design of Bioequivalence Study: Etoposide

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. For guidance on issues related to bioequivalence (BE) studies for immediate-release, solid oral dosage forms, see the ICH Harmonised Guideline M13A [Bioequivalence for Immediate-Release Solid Oral Dosage Forms](#) (2024). For BE issues outside the scope of the ICH M13A guideline, e.g., for additional strength biowaivers, 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 etoposide.

Pharmacokinetics of etoposide

On intravenous administration, the disposition of etoposide is best described as a biphasic process with a distribution half-life of about 1.5 hours and terminal elimination half-life ranging from 4 to 11 hours.

Total body clearance and the terminal elimination half-life are independent of dose over a range 100 to 600 mg/m². Over the same dose range, the areas under the plasma concentration vs. time curves (AUC) and the maximum plasma concentration (C_{max}) values increase linearly with dose.

Guidance for the design of bioequivalence studies

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

Design: A multiple-dose crossover design is recommended. The two periods of the BE study could be conducted in two consecutive cycles. Period I should begin on the first day of a treatment cycle. Pharmacokinetic sampling should take place on Day 5 of each period. Blood sampling should occur at the same time on Day 5 for both periods to assess the concentration-time curve at pre-dose (0 hour) and at appropriate post-dose sampling times. However, the feasibility of a single dose study could also be explored as described at doi: 10.5414/CP202223.

Dose: As the EoI includes 5 and 10 mg minitablets/coated multiparticulates, the bioequivalence study should be conducted with the highest strength if the waiver of the lowest strength applies. As the comparator is marketed at a different strength, the same dose of both products should be administered in the study periods.

The dose to be administered to the patients should be calculated on the basis of body surface area. The recommended dose of intravenous (IV) etoposide in small cell lung cancer is 35 mg/m²/day for 4 days to 50 mg/m²/day for 5 days. The oral dose of etoposide capsules is estimated as two times the IV dose rounded to the nearest 50 mg. Dosage should be adjusted based on the degree of myelosuppression produced. Each patient should receive his/her calculated dose with no change in dose between study periods, and concomitant medications should be the same for both periods of the study. If it becomes necessary to adjust a patient's dosing regimen, then that patient must be dropped from the bioequivalence study.

When conducting bioequivalence studies, it is essential to administer the test and the comparator product according to their corresponding instructions for use. In those cases where the test and the comparator product are different dosage forms with different methods of administration (e.g., a tablet that should be taken with a glass of water vs. minitables/coated multiparticulates to be swallowed with a small amount of water (e.g., 50 ml) since they are intended for children, the bioequivalence study should be conducted employing the intended method of administration of each product. It is considered incorrect to standardise the volume of liquid in all these cases (e.g., rinsing the container where the minitables/coated multiparticulates have been suspended with the remaining liquid of a glass of water) because this standardisation does not occur in real life conditions.

Fasted/fed: As the comparator product should be taken on an empty stomach, a fasted state study is recommended.

Subjects: Patients already receiving etoposide and expected to receive at least two additional cycles at the same dose. Furthermore, each patient should have comparable health status between the two periods of the 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 etoposide.

Sample size: According to Li and Liu, 2015 (doi: 10.5414/CP202223), the intra-subject CV(%) of $C_{\max}$ after a single dose in fasted state was 13% approximately.

Washout: If the study is conducted in two cycles of administration, the washout period between administration periods is the period between cycles.

Blood sampling: The blood sampling should be intensive for the first hours after administration to properly characterize the $C_{\max}$ of etoposide. Blood samples for the characterization of etoposide pharmacokinetics should cover one dosing interval, i.e., 24 h. In addition, pre-dose blood samples (at -48 h and -24 h) should be collected on the two previous days (day 3 and 4) of dosing in each period to ensure that steady-state blood plasma levels are achieved.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure etoposide in human plasma using LC-MS/MS analytical methodology. In the case of a single dose study, 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). See [Guideline on bioanalytical method validation and study sample analysis](#). In: WHO Technical Report Series, No. 1060, Annex 6, or the ICH Harmonised [Guideline M10](#) for more information on bioanalytical recommendations.

Statistical considerations: The data for etoposide should meet the following bioequivalence standards in a multiple-dose (in principle, but the possibility of a single dose study could be explored), crossover design study:

- The 90% confidence interval of the relative mean $AUC_{0-t,ss}$ of the test to comparator product should be within 80.00 – 125.00%.
- The 90% confidence interval of the relative mean $C_{\max,ss}$ of the test to comparator product should be within 80.00 – 125.00%.

Since patients will be receiving different dosing regimens, dose should be included in the statistical model. Correction for differing dosing regimens by dose-normalization is not recommended.