

Notes on the Design of Bioequivalence Study: Procarbazine

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 procarbazine.

Pharmacokinetics of procarbazine

Procarbazine is readily absorbed from the gastrointestinal tract. A plasma half-life of about 7 – 10 minutes has been reported. Its anticancer activity results from bioactivation to reactive intermediates. Procarbazine following systemic administration is first oxidized to azo-procarbazine and hydrogen peroxide by the cytochrome P450 system. The plasma half-life of azo-procarbazine ranges between 81 – 251 min.

Guidance for the design of bioequivalence studies

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

Design: A single dose crossover design is recommended.

Since procarbazine toxicity is cumulative, conducting the study during the early cycle of treatment reduces the likelihood of dropout due to toxicity. Since for the most part all regimens use the highest dose of procarbazine in the 1st week of a cycle, it is recommended to conduct the study on Days 1 and 2 of the 1st cycle.

Because nausea and vomiting are very common with this drug, it is not uncommon to use anti-emetic prophylaxis. This is acceptable, but the same prophylactic anti-emetic medication should be used before administration of both the test and reference products. Also, any concomitant medication should be exactly the same on both study days.

Dose: As the EoI includes 10 and 20 mg dispersible tablet, 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, i.e., 50 mg strength, the same dose of both products should be administered in the study periods.

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. a dispersible tablet to be dispersed in 30 – 50 mL of water), 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., 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. The maximum volume of water employed for a paediatric dispersible tablet should not exceed 50 ml.

Fasted/fed: As the comparator product can be taken with or without food, a fasted state study is recommended.

Subjects: Adult cancer patients receiving procarbazine or planning to receive a stable regimen using the same dosage unit (i.e. multiples of the same strength). Any patient for whom a procarbazine containing regimen is indicated could be enrolled, regardless of specific tumour type. Also, the investigators should adhere to the guidelines of a well-established standard-of-care regimen for the type of cancer being treated.

Due to its teratogenic effects, procarbazine should not be administered to women of child bearing potential unless they agree to remain celibate during the study or use some reliable form of birth control. Women who are surgically sterile or postmenopausal are recommended for the BE study.

Parent or metabolite data for assessment of bioequivalence: The parent drug is considered to best reflect the biopharmaceutical quality of the product. Therefore, bioequivalence should be based on the determination of procarbazine. However, as procarbazine is not active since it needs to be activated to reactive intermediates and its half-life is extremely short, which is expected to cause high variability, azo-procarbazine can also be used to demonstrate bioequivalence if high variability in procarbazine C_{max} or AUC_{0-t} is demonstrated. In such case, the results for both analytes should be reported.

Sample size: No information is currently available to PQT/MED on the intra-subject variability of procarbazine and azo-procarbazine in fasted state.

Washout: Due to the short half-life of procarbazine and its metabolite, the test and reference products can be studied on consecutive days with no additional washout period needed.

Blood sampling: The blood sampling should be intensive for the first minutes after administration to properly characterize the C_{max} of procarbazine and azo-procarbazine. Blood samples for the characterization of procarbazine and azo-procarbazine pharmacokinetics should not cover more than 1 h and 24 h, respectively. For example, samples can be taken pre-dose and at 0.08, 0.16, 0.25, 0.33, 0.42, 0.50, 0.58, 0.67, 0.75, 0.83, 0.92, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 5.0, 7.0, 9.0, 12.0, 16.0 and 20.0 hours after drug administration.

Analytical considerations: Information currently available to PQT/MED indicates that it is possible to measure procarbazine and azo-procarbazine 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). 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.

Statistical considerations: The data for procarbazine or azo-procarbazine, as predefined in the study protocol, 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 comparator product should be within 80.00 – 125.00%.
- The 90% confidence interval of the relative mean C_{max} of the test to comparator product should be within 80.00 – 125.00%.