Contains Nonbinding Recommendations

Draft Guidance on Procarbazine Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Procarbazine Hydrochloride

Form/Route: Capsule/Oral

Recommended study: 1 study

Type of study: Fasting
Design: Single-dose, two-way crossover *in-vivo*
Strength: EQ 50 mg base
Subjects: Cancer patients receiving procarbazine or planning to receive a stable regimen using the same dosage unit (i.e. multiples of the same strength). Since procarbazine toxicity is cumulative, conducting the study during the early cycle of treatment reduces the likelihood of dropout due to toxicity.
Additional Comments:

- Due to the short half life of procarbazine and its metabolite, the test and reference products can be studied on consecutive days with no washout period needed. Patients can continue to receive their standard dosing regimen post-study. 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 BE study on Days 1 and 2 of the 1st cycle
- Due to teratogenic effects, this drug 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
- Each patient should receive multiples of the designated 50 mg strength, with the same dose used in each period. 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 drugs. Also, any concomitant medication should be exactly the same on both study days.
- Investigators should refer to the Boxed Warning, Contraindications, Warnings, Precautions and Adverse Reactions in the FDA-approved labeling and follow the directions closely. Any patient for whom a procarbazine containing regimen is indicated could be enrolled, regardless of specific tumor type. Also, the investigators should adhere to the guidelines of a well-established standard-of-care regimen for the type of cancer being treated
- Submission of an Investigational New Drug Application (IND) is required prior to the conduct of a bioequivalence study for a cytotoxic drug product such as procarbazine (see 21 CFR § 320.31).

Analytes to measure (in appropriate biological fluid): Procarbazine, and its metabolite, azoprocarbazine, in plasma

Bioequivalence based on (90% CI): Procarbazine
Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Waiver request of in-vivo testing: Not applicable

Dissolution test method and sampling times:
Please note that a Dissolution Methods Database is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.