

Draft Guidance on Lomustine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Lomustine

Form/Route: Capsule/Oral

Recommended studies: 1 study

Design: Single-dose, two-way crossover in vivo

Strength: 40 mg

Subjects: Patients who are already receiving a stable dose of lomustine as described in the reference product label

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 lomustine (see 21 C.F.R. § 320.31).

Analytes to measure (in appropriate biological fluid): Cis-4-hydroxy lomustine and trans-4-hydroxy lomustine metabolites in plasma

Bioequivalence based on (90% CI): Cis-and trans-4-hydroxy lomustine metabolites

Waiver request of in vivo testing: 10 mg and 100 mg based on (i) acceptable bioequivalence studies on the 40 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

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.

Additional comments regarding the bioequivalence study:

- The patients shall receive their own established lomustine dosing regimen during the study as multiples of the 40 mg capsule. The dose administered to each subject should be the same between the two study periods. If dose adjustment is necessary between the test and reference doses then patients should be excluded from the study. After the study is completed, the patients should be continued on their current regimens for lomustine capsule. Since each patient in the study will be receiving different doses based on the

body surface area using multiples of the 40 mg strength, the dose based on body surface area should be included in the statistical model.

- Lomustine can be taken with or without food as prescribed. However, individual patient should follow the same regimen for both periods of the BE study.
- Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study.
- Monitor blood counts of patients weekly for at least six weeks after a dose. Investigators should refer to the Boxed Warning, Contraindications, Warnings, Precautions and Adverse Reactions in the FDA-approved labeling and follow the label recommendations closely.
- Cancer patients with monotherapy are generally recommended for the BE studies. However, cancer patients receiving concomitant drug(s) are allowed to participate, provided:
 - The concomitant medication is the same for both study arms and clearly documented.
 - The patients should follow the same dosing regimen for the concurrent medications for both periods of the BE study. Each concurrent medication should be well documented and clearly stated in the protocol.
 - Patients do not change their medications during the BE study.