

Draft Guidance on Altretamine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Capsule/Oral

Recommended studies: 1 study

Type of study: Steady-State

Design: Multiple-dose, two-way crossover *in-vivo*

Strength: Dose should be calculated on the basis of body surface area. Altretamine capsules may be administered at a dose of 260 mg/m²/day for 5 days. The total daily dose should be given as 4 divided oral doses after meals and at bedtime. The meals should be standardized, but there is no need to administer Altretamine with a high-fat meal.

Subjects: Patients with persistent or recurring ovarian cancer following first-line therapy with a cisplatin and/or alkylating agent-based combination already on altretamine or previously determined to be candidates for such therapy.

Additional Comments:

- 1) 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 Altretamine (see 21 CFR §320.31).
- 2) Period I can begin on the first day of treatment cycle. Pharmacokinetic sampling should take place on Day 5 of Period I and II. Blood sampling should occur over a dosing interval on the Day 5 morning to assess the concentration-time curve at pre-dose (0 hour) and at appropriate post-dose sampling time. Following end of Period I pharmacokinetic sampling day, patients should be switched to receive the other treatment in Period 2. Patients should be dosed for another 5 days prior to pharmacokinetic sampling for Period II. Both periods of the bioequivalence studies should be completed within one treatment cycle of Altretamine Capsules.
- 3) Blood samples should be collected on the last three days (day 3, 4 and 5) of dosing in each period to ensure that steady-state blood plasma/serum levels are achieved. Attainment of steady state can be verified by regression analysis. The pre-dose blood sampling must include at least three successive trough level samples (C_{min}).
- 4) Applicants may consider using a reference-scaled average bioequivalence approach for this highly variable drug substance/product. Please provide evidence of high variability in the bioequivalence parameters, AUC and/or C_{max} (i.e., within-subject variability ≥30%) when using this approach. For general information on this approach, please refer to

Haidar et al., Bioequivalence Approaches for Highly Variable Drugs and Drug Products, Pharm. Res. 25:237-241(2008). To avoid variability from different treatment cycles, all the periods of the bioequivalence studies should be conducted within the same treatment cycle.

- 5) After the study is completed, patients should be continued on their current dose of Altretamine.
- 6) 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.
- 7) If it becomes necessary to adjust a patient's dosing regimen, then that patient must be dropped from the bioequivalence study.

Analytes to measure (in appropriate biological fluid): Altretamine and its metabolites pentamethylmelamine and tetramethylmelamine in plasma

Bioequivalence based on (90% CI): Altretamine

Please submit the metabolites data as supportive evidence of comparable therapeutic outcome. For the metabolites, pentamethylmelamine and tetramethylmelamine, 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/index.cfm>. 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.