Contains Nonbinding Recommendations

Draft Guidance on Etoposide

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Capsule/Oral

Recommended studies: 1 study

1. 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. The recommended dose of intravenous (IV) etoposide in small cell lung caner is 35 mg/m^2/day for 4 days to 50 mg/m^2/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.

   Subjects: patients already receiving etoposide and expected to receive at least two additional cycles at the same dose. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.

   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 Etoposide (see 21 CFR §320.31).

   2) The two-periods of the BE study should be conducted in two consecutive cycles. 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.

   3) Period I can 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. The patients should be switched to receive the other treatment in Period II.

   4) 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 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 (Cmin).

5) After the study is completed, patients should be continued on their current dose of Etoposide.

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.

Analytes to measure (in appropriate biological fluid): Etoposide in plasma

Bioequivalence based on (90% CI): Etoposide

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.