Contains Nonbinding Recommendations

Draft Guidance on Topotecan Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Capsule /Oral

Recommended studies: 2 Studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 0.25 mg; Dose at the rate of 2.3 mg/m^2
   Subjects: cancer patients with relapsed small cell lung cancer with a prior complete or partial response and who are at least 45 days from the end of first-line chemotherapy.
   Additional Comments: see below

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2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 0.25 mg; Dose at the rate of 2.3 mg/m^2
   Subjects: Cancer patients with relapsed small cell lung cancer with a prior complete or partial response and who are at least 45 days from the end of first-line chemotherapy.
   Additional Comments: Please refer to the Amantadine hydrochloride tablets for information regarding fed studies. The following recommendations apply to both fasting and fed studies:

   a. Patients shaould receive their own established topotecan dosing regimen during the study as multiples of the 0.25 mg capsule. The dose administered to each patient should be the same between the two study periods. After the study is completed, patients should be continued on their current regimen of topotecan capsules. Since each patient in the study will be receiving different doses, dose should be included in the statistical model. Correction for differing dosing regimens by dose-normalization is not recommended.

   b. Due to the short half-life of Topotecan (3-6 hours), the test and reference products may be dosed on two consecutive days of a treatment cycle. If the products are administered on two consecutive days, the test product and RLD treatments should be administered at the same time of the day, e.g., both in the morning (or both in the evening) of Day-1 (Period I of the study) and Day-2 (Period 2 of the study).

c. According to the labeling, the patients should be dosed with 2.3 mg/m^2/day on two consecutive days. Thus, in a treatment cycle on Day-1 (Period-1), half of the subjects should be dosed with Test and the other half with Reference product, followed on Day-2 of the same Treatment cycle (Period 2) by dosing with reference and test, respectively, in a crossover manner.

d. Each of the BE studies should be conducted **entirely** using multiples of the 0.25 mg strength capsules. Please screen for subjects using multiples of the 0.25 mg dose only, without any adjustments.

e. Since there may be a high percentage of dropouts (20-25%) due to adverse reactions, etc., please recruit an adequate number of patients in the study to achieve sufficient statistical power.

f. Additionally, in order to reduce the number of dropouts, we recommend recruitment of patients who have gone through at least one or two treatment cycles, and preferably three treatment cycles.

g. Since topotecan is a cytotoxic drug, please submit an Investigational New Drug Application (IND) per 21 § CFR 320.31(a)(3) prior to the conduct of bioequivalence studies.

Analytes to measure (in appropriate biological fluid): Topotecan lactone and total topotecan in plasma

Bioequivalence based on (90% CI): Topotecan lactone

Please submit total topotecan data as supportive evidence.

Waiver request of in-vivo testing:

Topotecan capsule, 1 mg strength may be considered for a waiver of in vivo bioequivalence study based on: (1) acceptable bioequivalence studies on the 0.25 mg strength, (2) acceptable dissolution testing on the 0.25 and 1.0 mg strengths, and (3) proportional similarity in the formulations of the 0.25 and 1 mg 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/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.