Contains Nonbinding Recommendations

Draft Guidance on Lapatinib Ditosylate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablets/Oral

Recommended studies: 1 study

Type of study: Steady state
Design: Two-way, crossover *in vivo*
Strength: 250 mg (Dose 5 x 250 mg base once daily)
Subjects: Patients with advanced or metastatic breast cancer for whom the drug is indicated in combination with capecitabine.
Additional Comments: Specific recommendations are provided below.

IND submission:

Submission of an Investigational New Drug Application (IND) is required prior to conduct of a bioequivalence study that involves a cytotoxic drug product (21CFR320.31). Although lapatinib is not cytotoxic, the product is co-administered with capecitabine, which is a prodrug of 5-fluorouracil, which is cytotoxic. Therefore, an IND must be submitted prior to conduct of the recommended bioequivalence study for lapatinib.

Analytes to measure (in appropriate biological fluids): Lapatinib in plasma

Bioequivalence based on (90% CI): Lapatinib

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times:
Please note that a **Dissolution Method 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 PK bioequivalence study:

1. Subjects should be patients who are already on a regimen of oral lapatinib ditosylate tablets in combination with capecitabine, and who have been through at least one complete 21 day cycle prior to enrollment in the study.

2. Patients with rapidly progressing disease, especially with visceral organ involvement, should not be entered into the study.

3. Women of childbearing potential and nursing mothers should be excluded from study, given the potential for embryo-fetal toxicity and secretion of the drug into the milk.

4. Males and their female partners need to practice adequate contraception for at least 1 week after the last lapatinib dose.

5. The usual inclusion/exclusion criteria regarding acceptable hepatic function and limiting of concomitant medications that could result in metabolic drug interactions are recommended.

6. Patients with significant hepatic dysfunction, or for whom the need for dose changes during the study can be anticipated, should be excluded.

7. As part of the subject's scheduled therapy, each patient would receive their dose of lapatinib ditosylate using either the test or reference product in a crossover design in consecutive 21 day cycles. Pharmacokinetic sampling in each cycle is recommended during the 7 day period when capecitabine is not co-administered, as described below.

8. Lapatinib is dosed once daily on Days 1-21 continuously in combination with capecitabine dosed twice daily on Days 1-14 in a repeating 21 day cycle. Due to the tendency of lapatinib AUC_{tau} and C_{max} to be higher upon co-administration of capecitabine, we recommend determination of lapatinib AUC_{tau} and C_{max} at steady state during the latter part of the 7 day period when capecitabine is not co-administered (3-5 lapatinib elimination half-lives after the last dose of capecitabine in that cycle of treatment). Due to its short elimination half-life, pharmacokinetic washout of capecitabine will also have occurred before the attainment of lapatinib steady state in the latter part of the 7 day period. Consecutive lapatinib trough levels are recommended to establish attainment of steady state.

9. Consistent with labeling, lapatinib should be taken at least one hour before or one hour after a meal.

10. Any concomitant medications taken by a patient should be the same for the two study periods. If a change in concomitant medications is necessary, that subject should be dropped from the study.

11. No changes in dose or regimen should be made for the purpose of the bioequivalence study.