

Draft Guidance on Lamotrigine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Lamotrigine

Dosage Form; Route: Extended-release tablet; oral

Recommended Studies: Three studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 200 mg
Subjects: Healthy males and females (nonpregnant), general population.
Additional Comments: Subjects with a history of any prior allergic drug rash should be excluded from the study. If a subject develops a rash, the subject should be discontinued from the study. Adverse events from bioequivalence (BE) studies should be collected, described in detail, and submitted to FDA with the study reports and data. In addition, the Informed Consent (IC) should provide adequate information. Specifically, the IC should prominently state that: (1) lamotrigine extended-release may cause a serious skin rash that may cause hospitalization or even death, (2) there is no way to tell if a mild rash will become more serious, (3) a serious skin rash can happen at any time during treatment.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 200 mg
Subjects: Healthy males and females (nonpregnant), general population.
Additional Comments: See comments above.

3. Type of study: Fasting
Design: Single-dose, two-way, crossover in vivo
Strength: 50 mg
Subjects: Healthy males and females (nonpregnant), general population.
Additional Comments: See comments above.

Analytes to measure (in appropriate biological fluid): Lamotrigine in plasma*

* Please utilize a validated analytical method such as LC-MS/MS to reliably measure plasma lamotrigine concentrations. A lower limit of quantitation of 10 ng/mL is recommended to adequately characterize the pharmacokinetics at 50 mg study dose.

Bioequivalence based on (90% CI): Lamotrigine

Waiver request of in vivo testing: 25 mg based on (i) acceptable BE study on the 50 mg strength; (ii) proportional similarity of the formulations on 25 mg and 50 mg strengths; (iii) acceptable in vitro dissolution testing of 25 mg and 50 mg strengths.

100 mg, 250 mg, and 300 mg strengths based on: (i) acceptable BE studies on the 200 mg strength; (ii) proportional similarity of the formulations across 100 mg, 200 mg, 250 mg, and 300 mg strengths; (iii) acceptable in vitro dissolution testing for the 100 mg, 200 mg, 250 mg, and 300 mg strengths.

Dissolution test method and sampling times:

The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. 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 abbreviated new drug application.

For modified-release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) and water should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: one, two, and four hours, and every two hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 tablets. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose-dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 2 (paddle) at 50 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Both test and reference listed drug products must be tested accordingly and data must be provided on individual unit, means, range, and %CV on all strengths.