

Draft Guidance on Nevirapine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Extended Release Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, randomized, two treatment, one-period, parallel, open-label in vivo
Strength: 400 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Due to safety concerns of severe life-threatening skin reactions and hepatotoxicity, single dose parallel study designs in healthy volunteers are recommended.

2. Type of study: Fed
Design: Single-dose, randomized, two treatment, one-period, parallel, open-label in vivo
Strength: 400 mg
Subjects: Healthy males and nonpregnant females, general population.
Additional Comments: Please see comments above
Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed study.

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

Bioequivalence based on (90% CI): Nevirapine

Waiver request of in vivo testing: 100 mg based on (i) acceptable bioequivalence studies on the 400 mg strength, (ii) acceptable dissolution testing across both strengths, and (iii) proportional similarity in the formulations across both 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/>. 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.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products 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) 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. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, apparatus I (basket) @ 75 rpm, with and without the alcohol (see below):

Test 1: 12 units tested according to the proposed method (with 0.1 N 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 strengths of the test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on both strengths.