Contains Nonbinding Recommendations

Draft Guidance on Duloxetine Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Duloxetine hydrochloride

Dosage Form; Route: Delayed release capsule; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 60 mg Base
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

---

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 60 mg Base
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

---

3. Type of study: Fasting, sprinkle-in-applesauce
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 60 mg Base
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

Analyte to measure (in appropriate biological fluid): Duloxetine in plasma

Bioequivalence based on (90% CI): Duloxetine

Additional strengths: Bioequivalence of the EQ 20 mg Base, EQ 30 mg Base, and EQ 40 mg Base strengths to the corresponding reference product strengths may be demonstrated based on principles laid out in the FDA guidance on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*

Dissolution test method and sampling times:

For modified release drug products, FDA recommends that applicants develop specific discriminating dissolution methods. Applicants may also use the dissolution method set forth in any related official United States Pharmacopeia (USP) drug product monograph, or in the FDA's database (available at http://www.accessdata.fda.gov/scripts/cder/dissolution/) provided that Applicants submit adequate dissolution data supporting the discriminating ability of such a method. If a new dissolution method is developed for the modified release drug product, FDA recommends that the submission includes the dissolution method development and validation report with the complete information/data supporting the proposed method. Conduct comparative dissolution testing on 12 dosage units for each strength of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

In vitro alcohol dose dumping testing:
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: 1000 mL, 0.1 N HCl, USP apparatus I (basket) at 100 rpm, with or without alcohol:

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

Submit standard operating procedures (SOPs) for the testing method, individual dissolution data of duloxetine, percent of breakdown products (1-naphthol, and 1,4-rearrangement compound) at each time point, mean values, standard deviations, coefficient of variation (%CV), and plots of the percent release profiles of duloxetine, 1-naphthol, and 1,4-rearrangement compound over the 2-hour period.

In vitro 6-hour stability testing:
Due to concerns that patients with a delayed gastric emptying time may experience release of duloxetine in the stomach, leading to the formation of 1-naphthol, a toxic compound, applicants should conduct comparative in vitro stability testing on all strengths of the test and reference products (12 units each) using the following method:

Testing Method: 0.1 N HCl, 1000 mL (without alcohol), USP apparatus I (basket) at 100 rpm, for 6 hours

Submit SOPs for the testing method, individual dissolution data for duloxetine, percent of breakdown products (1-naphthol, and 1,4-rearrangement compound) at each time point, mean values, standard deviations, %CV, and plots of the percent release profiles of duloxetine, 1-naphthol, and 1,4-rearrangement compound over the 6-hour period.

Product-specific testing conditions for in vitro feeding tube studies:
The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) tube. Conduct the in vitro feeding tube studies including comparative recovery testing, particle size distribution study, comparative acid resistance stability testing, and sedimentation volume testing. Refer to the Lansoprazole Delayed-Release Orally Disintegrating Tablet Guidance for additional information regarding procedures of in vitro feeding tube studies.

Testing tube: NG tube (12 French)

Testing strength: EQ 60 mg Base

Dispersion medium: 50 mL water with different pH values (e.g., pH 5.5, 7.0 and 8.5)

Testing conditions for acid resistance stability testing: 1000 mL of 0.1 N HCl maintained at 37 ± 0.5°C; USP Apparatus I at 100 rpm. Analyze the amount of duloxetine, 1-naphthol, and 1,4-rearrangement compound at 120 minutes.