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Draft Guidance on Duloxetine Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 60 mg Base
   Subject: Males and non-pregnant, non-lactating females, general population
   Additional comments: Due to the need to maintain the enteric coating, the subjects in a bioequivalence (BE) study should be advised to swallow the capsule whole.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 60 mg Base
   Subject: Males and non-pregnant, non-lactating females, general population
   Additional comments: See above.

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

Bioequivalence based on (90% CI): Duloxetine

Additional strengths: BE of EQ 20 mg Base, EQ 30 mg Base, and EQ 40 mg Base[1] 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

[1] Note that there is no Reference Listed Drug (RLD) for the EQ 40 mg Base strength listed in the Orange Book. For additional information on this strength, refer to the FDA response to Citizen Petition, Docket No. FDA-2010-P-0535, which is available to the public at http://www.regulations.gov.

adequate dissolution data support 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 each of all strengths of the test and reference products. Specifications will be determined upon review of the 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 the alcohol:
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> **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
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> **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
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> **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 empting time may experience release of duloxetine in the stomach, leading to the formation of 1-naphthol, a toxic compound, you should conduct comparative in vitro stability testing on all strengths of the test and RLD 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, coefficient of variation (%CV), and plots of the percent release profiles of duloxetine, 1-naphthol, and 1,4-rearrangement compound over the 6-hour period.