Contains Nonbinding Recommendations

Draft Guidance on Venlafaxine Hydrochloride

Active ingredient: Venlafaxine Hydrochloride

Form/Route: Extended Release Capsule /Oral

Recommended studies: 2 studies

1. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 150 mg
   Subjects: Normal healthy males and females, general population
   Additional Comments: Due to safety concerns, bioequivalence studies under fasting conditions are not recommended.

---

2. Type of study: Fed Sprinkle
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 150 mg
   Subjects: Normal healthy males and females, general population
   Additional comments: Please administer the dose after sprinkling the entire contents of the capsule on a teaspoonful of applesauce in accordance with the approved labeling of the reference product under fed conditions.
   Please see comment above.

Analytes to measure: Venlafaxine, and its metabolite O-desmethylvenlafaxine, in plasma.

Bioequivalence based on (90% CI): Venlafaxine

Waiver request of in-vivo testing: 37.5 mg and 75 mg based on (i) acceptable bioequivalence studies on the 150 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all 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.fda.gov/cder/ogd/index.htm. 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 a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional in vitro 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 I (basket) at 100 rpm, with and 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

All strengths of the test and the corresponding reference products must be tested accordingly and data must be provided on individual unit, means, range and %CV including f2 similarity values and dissolution plots.