Contains Nonbinding Recommendations

Draft Guidance on Diltiazem Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended release capsule; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 420 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 420 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

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3. Type of study: Fasting sprinkle-in-applesauce
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 420 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

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

Bioequivalence based on (90% CI): Diltiazem

Additional strengths: Bioequivalence of 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg 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, applicants should develop specific discriminating dissolution methods. Applicants may 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, the dissolution method development and validation report with the complete information/data supporting the proposed method should be submitted. 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 addition to the method above, dissolution profiles on 12 dosage units for each strength of the test and reference products generated using USP Apparatus 1 at 100 rpm and/or Apparatus 2 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted. Agitation speeds may be increased if appropriate. It is acceptable to add a small amount of surfactant if necessary. 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.