Contains Nonbinding Recommendations

Draft Guidance on Metoprolol Succinate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: EQ 200 mg Tartrate
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: None

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 200 mg Tartrate
   Subjects: Healthy males and non-pregnant, non-lactating females
   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: EQ 200 mg Tartrate
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: None

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

Bioequivalence based on (90% CI): Metoprolol

Waiver request of in vivo testing: EQ 25 mg, 50 mg, and 100 mg Tartrate based on (i) acceptable bioequivalence studies on the EQ 200 mg Tartrate 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: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the

public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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 abbreviated new drug application (ANDA).

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. 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.

Due to concerns of dose dumping from this drug product when taken with alcohol, conduct additional dissolution testing on **all strengths** using various concentrations of ethanol in the dissolution medium, as follows:
Testing Conditions: 500 mL, 0.1 N HCl, USP apparatus 2 (paddle) at 50 rpm, with or 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.

Both test and RLD products should be tested accordingly and data should be provided on individual unit, means, range and %CV.

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 (12 French or larger). Conduct the in vitro feeding tube studies including comparative recovery testing, particle size distribution study, 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 200 mg Tartrate

Dispersion medium: 15 mL water with different pH values (e.g., pH 5.5, 7.0 and 8.5)