Contains Nonbinding Recommendations

Draft Guidance on Nisoldipine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form/Route: Extended release tablets; oral

Recommended studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 40 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: Carefully monitor the subjects' blood pressure and heart rates during the study, particularly over the first 10 hours.

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2. Type of study: Fasting
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 20 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: See above.

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3. Type of study: Fed
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 20 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional Comments: The recommendation on the lowest dose (20 mg) was based on the safety consideration of conducting a fed study in healthy subjects. The subjects' blood pressure and heart rates need to be carefully monitored during the entire course of the fed study, particularly over the first 14 hours. Obtain blood pressure and heart rate hourly until 8 hours post-dose, then every 2 hours until 14 hours post-dose. Be advised for the following inclusion/exclusion criteria for the subject enrollment (sponsor may add additional criteria).

   Inclusion Criteria:
   - Males and non-pregnant, non-lactating females, 18 to 65 years of age
   - No prior history of cardiovascular signs, symptoms, conditions, or diseases
   - Baseline systolic blood pressure ≥ 110 mm Hg and diastolic blood pressure ≥ 60 mmHg

Exclusion Criteria:

- Patients currently taking medications or supplements that are known to cause systemic hypotension.

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

Bioequivalence based on (90% CI): Nisoldipine

Waiver request of in-vivo testing: 30 mg based on (i) acceptable bioequivalence studies on the 40 mg and 20 mg strengths, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity in the formulations across all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website 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).

For modified release products, dissolution profiles 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, water) 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. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets. Specifications will be determined upon review of the data submitted in the application.