Contains Nonbinding Recommendations

Draft Guidance on Chlorpheniramine Polistirex; Codeine Polistirex

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended-release suspension; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: Chlorpheniramine polistirex/codeine polistirex Eq. to 2.8 mg base per 5 mL/Eq. to 14.7 mg base per 5 mL
   Subjects: Healthy males and females, general population, aged 18 to 55 years
   Additional comments: Females should not be pregnant or breastfeeding

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: Chlorpheniramine polistirex/codeine polistirex Eq. to 2.8 mg base per 5 mL/Eq. to 14.7 mg base per 5 mL
   Subjects: Healthy males and females, general population, aged 18 to 55 years
   Additional comments: Females should not be pregnant or breastfeeding

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Analytes to measure (in appropriate biological fluid): Chlorpheniramine and codeine in plasma

Bioequivalence based on (90% CI): Chlorpheniramine and codeine

Waiver request of in-vivo testing: Not applicable

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/. Note that a dosage unit for a suspension is the labeled strength (5 mL). A total of 12 units from 12 different bottles should be used for the test and reference products, respectively. 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 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.

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: 900 mL, 0.1 N HCl, USP apparatus II (paddle) @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 must be tested accordingly and data must be provided on individual unit, means, range and %CV.