Contains Nonbinding Recommendations

Draft Guidance on Propafenone Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Extended release capsules; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 425 mg
   Subjects: Healthy 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-way crossover in-vivo
   Strength: 425 mg
   Subjects: Healthy males and non-pregnant, non-lactating females, general population.
   Additional Comments: None

Special Considerations: Applicants may consider using a reference-scaled average bioequivalence approach for propafenone. If using this approach, the applicant should provide evidence, from their studies, of high variability (i.e., within-subject variability $\geq 30\%$) in bioequivalence parameters. For general information on this approach, applicants are encouraged to refer to Draft Guidance on Progesterone Capsule/Oral recommended April 2010 and revised February 2011.

Analytes to measure (in appropriate biological fluid): Propafenone and its metabolite 5-OH propafenone in plasma.

Bioequivalence based on (90% CI): Propafenone

Please submit the metabolite data for 5-OH propafenone as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Waiver request of in-vivo testing: 225 mg and 325 mg based on (i) acceptable bioequivalence studies on the 425 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: 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. 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.