Draft Guidance on Fesoterodine Fumarate

Active ingredient: Fesoterodine Fumarate

Form/Route: Extended Release Tablet/Oral

Recommended study: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two way crossover in-vivo
   Strength: 8 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional Comments:

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2. Type of study: Fed
   Design: Single-dose, two way crossover in-vivo
   Strength: 8 mg
   Subjects: Healthy males and nonpregnant females, general population
   Additional Comments:

Analytes to measure (in appropriate biological fluid): Fesoterodine and its active metabolite, 5-HMT in plasma.

Bioequivalence based on (90% CI): Fesoterodine.

Please use fesoterodine plasma concentrations for bioequivalence determination and analyze the fesoterodine AUC and Cmax data using the confidence interval approach if its plasma concentrations can be reliably measured and its pharmacokinetic parameters accurately determined. The data for the active metabolite (5-HMT) can be used to provide 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.

If it is not possible to measure fesoterodine in plasma accurately and reliably, then the bioequivalence determination will be based on the 5-HMT AUC and Cmax data, which will be analyzed using the confidence interval approach.

Waiver request of in-vivo testing: 4 mg based on (i) acceptable bioequivalence studies on the 8 mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please 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 application.

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.

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 2 (paddle) @75 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 on both strengths.