Draft Guidance on Tolterodine Tartrate

Contains Nonbinding Recommendations

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Tolterodine Tartrate

Form/Route: Extended-Release Capsules/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in-vivo
   Strength: 4 mg
   Subjects: Healthy males and females, general population
   Additional Comments:

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in-vivo
   Strength: 4 mg
   Subjects: Normal healthy males and females, general population
   Additional comments:

Analytes to measure (in appropriate biological fluid): Tolterodine and the 5-hydroxymethyl tolterodine (5-OHM) metabolite in plasma.

As for all other systemically available drugs, the respective Tmax data for tolterodine and the 5-hydroxymethyl tolterodine (5-OHM) metabolite from the Test and Reference products will be evaluated as supportive evidence of bioequivalence and for any clinically significant difference.

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.

Bioequivalence based on (90% CI): Tolterodine

Waiver request of in-vivo testing: 2 mg, based on (i) acceptable bioequivalence studies on the 4 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:

Please note that a Dissolution Methods Database is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. 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.

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.