Contains Nonbinding Recommendations

Draft Guidance on Estrogens, Conjugated Synthetic A

Active ingredient: Synthetic Conjugated Estrogens, A

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1.25 mg
   Subjects: Healthy, physiologically or surgically postmenopausal females.
   Additional Comments: None

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2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1.25 mg
   Subjects: Healthy, physiologically or surgically postmenopausal females.
   Additional Comments: None

Analytes to measure (in appropriate biological fluid): Unconjugated estrone, total estrone, unconjugated equilin and total equilin in plasma.

Please provide baseline correction for unconjugated and total estrone in the analysis. Please measure baseline unconjugated and total estrone levels at -48, 24, and 0 hours. The mean of the pre-dose unconjugated and total estrone levels should be used for the baseline adjustment of the post-dose levels. Any negative values obtained from baseline correction should be designated as zero (0) and any subject with baseline-adjusted pre-dose concentrations (at time 0 hour) greater than 5% of their Cmax should be excluded from the bioequivalence statistical analysis and the 90% confidence interval based on the remaining subjects.

Bioequivalence based on (90% CI): Baseline-adjusted unconjugated estrone, baseline-adjusted total estrone, unconjugated equilin, total equilin.

Waiver request of in-vivo testing: 0.3 mg, 0.45 mg, 0.625 mg and 0.9 mg based on (i) acceptable *in-vivo* bioequivalence study on the 1.25 mg strength, (ii) formulations of all strengths are proportionally similar and (iii) acceptable dissolution testing for 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, 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.