Contains Nonbinding Recommendations

Draft Guidance on Estradiol; Norethindrone Acetate

Active ingredient: Estradiol; Norethindrone Acetate

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1.0 mg; 0.5 mg
   Subjects: Healthy postmenopausal women
   Additional Comments:

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2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 1.0 mg; 0.5 mg
   Subjects: Healthy postmenopausal women
   Additional Comments:

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

Please measure baseline levels of unconjugated estradiol, unconjugated estrone and total estrone in plasma at -1.0, -0.5, and 0 hours before dosing. The mean of the pre-dose levels of unconjugated estradiol, unconjugated estrone and total estrone should be used for the baseline adjustment of the post-dose levels. For each subject, baseline concentrations should be determined for each dosing period, and baseline adjustments should be period specific. If a negative plasma concentration value results after baseline adjustments, this should be set to 0 prior to calculating the baseline-adjusted AUC.

Bioequivalence based on (90% CI): Norethindrone and baseline-adjusted total estrone

Statistical analysis should be performed on data both with and without baseline adjustment. Bioequivalence acceptance criteria will be based on norethindrone and baseline-adjusted total estrone results only. Please provide the data for unconjugated estradiol and unconjugated estrone as supportive evidence of comparable therapeutic outcome. For unconjugated estradiol and unconjugated estrone, 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: 0.5 mg/0.1 mg based on (i) acceptable bioequivalence studies on the 1 mg/0.5 mg strength, (ii) acceptable dissolution testing across all strengths, and (iii) proportional similarity in 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.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.