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Draft Guidance on Estradiol; Norethindrone Acetate

October 2024

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Active Ingredients: Estradiol; Norethindrone acetate

Dosage Form: Tablet

Route: Oral

Strengths: 0.5 mg; 0.1 mg, 1.0 mg; 0.5 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1.0 mg; 0.5 mg
   Subjects: Healthy postmenopausal females
   Additional comments: None

Analytes to measure: Estradiol (unconjugated), estrone (total), estrone (unconjugated), and norethindrone in plasma

Measure baseline concentrations 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 concentrations of unconjugated estradiol, unconjugated estrone and total estrone should be used for the baseline adjustment of the post-dose concentrations. 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 area under the curve.

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. 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 C_{max}.

Waiver request of in vivo testing: 0.5 mg; 0.1 mg strength based on (i) acceptable bioequivalence study on the 1 mg; 0.5 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution. Conduct comparative dissolution testing on 12 dosage units for each of both strengths of the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the abbreviated new drug application.

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[1] If the reference listed drug is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*