Contains Nonbinding Recommendations

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Draft Guidance on Estradiol; Progesterone

December 2025

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Active Ingredients: Estradiol; Progesterone

Dosage Form: Capsule

Route: Oral

Strengths: 0.5 mg; 100 mg and 1 mg; 100 mg

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1 mg; 100 mg
   Subjects: Healthy postmenopausal females
   Additional comments: None

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1 mg; 100 mg
   Subjects: Healthy postmenopausal females
   Additional comments: None

Analytes to measure: Unconjugated estradiol and progesterone in plasma

Measure baseline unconjugated estradiol concentrations at -1, -0.5, and 0 hours before dosing. The mean of the pre-dose unconjugated estradiol concentrations should be used for the baseline correction. Pharmacokinetics and statistical analyses should be performed on both baseline uncorrected and baseline corrected data.

Bioequivalence based on (90% CI): Baseline-corrected unconjugated estradiol and progesterone

Waiver request of in vivo testing: 0.5 mg; 100 mg strength based on (i) acceptable bioequivalence studies on the 1 mg; 100 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 evaluation of the abbreviated new drug application.

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Unique Agency Identifier: PSG_210132

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