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Draft Guidance on Dienogest; Estradiol Valerate

October 2024

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Active Ingredients: Dienogest; Estradiol valerate

Dosage Form: Tablet

Route: Oral

Strengths: N/A, 2 mg, 3 mg, N/A, N/A; 3 mg, 2 mg, 2 mg, 1 mg, N/A

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: 3 mg; 2 mg tablet of dienogest and estradiol valerate
   Subjects: Healthy postmenopausal females
   Additional comments: None

2. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 3 mg tablet of estradiol valerate
   Subjects: Healthy postmenopausal females
   Additional comments: None

Analytes to measure: Dienogest, estradiol, unconjugated estrone, total estrone in plasma for combination tablets. Estradiol, unconjugated estrone, total estrone for the single component tablet

Provide baseline correction for endogenous estradiol, unconjugated estrone and total estrone in the analysis. Measure baseline estradiol, unconjugated estrone and total estrone concentrations at -1, -0.5 and 0 hours.

Bioequivalence based on (90% CI): Dienogest 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 baseline-adjusted results only.

Waiver request of in vivo testing: Dienogest; estradiol valerate tablets, 2 mg; 2 mg strength based on (i) acceptable bioequivalence study on the 3 mg; 2 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

Estradiol valerate tablets, 1 mg strength based on (i) acceptable bioequivalence study on the 3 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 all 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 RLD is not available, refer to the most recent version of the FDA guidance for industry on *Referencing Approved Drug Products in ANDA Submissions.*