Contains Nonbinding Recommendations

Draft Guidance on Dienogest; Estradiol Valerate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Dienogest;Estradiol Valerate

Form/Route: Tablets/Oral

Recommended studies: 3 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 3 mg/ 2 mg tablet of dienogest and estradiol valerate
   Subjects: Healthy postmenopausal women
   Additional Comments:

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: 3 mg/ 2 mg tablet of dienogest and estradiol valerate
   Subjects: Healthy postmenopausal women
   Additional Comments:

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3. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 3 mg tablet of estradiol valerate
   Subjects: Healthy postmenopausal women
   Additional Comments:

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

Please provide baseline correction for endogenous estradiol, unconjugated estrone and total estrone in the analysis. Please measure baseline estradiol, unconjugated estrone and total estrone levels at -1, -0.5 and 0 hours. The mean of the pre-dose 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): 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 based on (i) acceptable bioequivalence studies on the 3 mg/2 mg strength, (ii) the formulations are proportionally similar, and (iii) acceptable *in vitro* dissolution testing of both strengths.

Estradiol Valerate Tablets, 1 mg based on (i) acceptable bioequivalence studies on the 3 mg strength, (ii) the formulations are proportionally similar, and (iii) acceptable *in vitro* dissolution testing of both 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.