

Draft Guidance on Drospirenone; Estradiol

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Drospirenone; Estradiol

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 0.5 mg/1 mg
Subjects: Normal healthy postmenopausal women
Additional Comments: N/A
2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 0.5 mg/1 mg
Subjects: Normal healthy postmenopausal women
Additional Comments: N/A

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

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

Submit the unconjugated estradiol and unconjugated estrone data as supportive evidence of comparable therapeutic outcome. For the 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}.

Statistical analysis should be performed on data both with and without baseline adjustment. Bioequivalence acceptance criteria will be based on baseline-adjusted results only.

Baseline adjustment: Data of each subject and period should be adjusted for the mean of -1 hour, -0.5 hour and pre-dose levels for that same subject and period. If, after adjustment, any negative concentrations result, they should be set equal to zero.

Waiver request of in vivo testing: 0.25 mg/0.5 mg based on (i) acceptable bioequivalence studies on the 0.5 mg/1 mg strength, (ii) acceptable dissolution testing on all strengths, and (3) proportional similarity in the formulations across all strengths. If only the lower strength, 0.25

mg/0.5 mg is to be marketed first, then the fasting and fed studies should be conducted on this lower strength, comparing it with the equal strength of the reference listed drug (RLD) product. However, if the higher strength, 0.5 mg/1 mg, is to be marketed following the in vivo studies of the lower strength, then an additional fasting study will be requested for the higher strength.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods Web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. 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 abbreviated new drug application.