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Draft Guidance on Drospirenone; Estradiol

October 2024

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Active Ingredients: Drospirenone; Estradiol

Dosage Form: Tablet

Route: Oral

Strengths: 0.25 mg; 0.5 mg, 0.5 mg;1 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: 0.5 mg; 1 mg
   Subjects: Healthy postmenopausal females
   Additional comments: None

Analytes to measure: Drospirenone and unconjugated estradiol, unconjugated estrone and total estrone in plasma

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}.

Bioequivalence based on (90% CI): Drospirenone 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.

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 study on the 0.5 mg; 1 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations between both strengths. If only the lower strength, 0.25 mg; 0.5 mg is to be marketed first, then the study 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 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 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.*