Contains Nonbinding Recommendations

Draft Guidance on Drospirenone; Ethinyl Estradiol; Levomefolate Calcium

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Drospirenone; Ethinyl Estradiol; Levomefolate Calcium

Form/Route: Tablet; Oral

Recommended studies: 3 Studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 3 mg/0.03 mg/0.451 mg tablet of drospirenone, ethinyl estradiol and levomefolate calcium
   Subjects: Healthy nonpregnant females, general population
   Additional Comments: To minimize folate intake, meals containing negligible amount of folate should be provided to subjects during the confinement period. Please measure and report the total folate content of each meal provided during the study period.

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2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 3 mg/0.03 mg/0.451 mg tablet of drospirenone, ethinyl estradiol and levomefolate calcium
   Subjects: Healthy nonpregnant females, general population
   Additional Comments: Please see above. For information regarding the calorie composition of the high-fat meal used for the fed study please refer to the specific product guidance for Amantadine Hydrochloride Tablets.

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3. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 0.451 mg tablet of levomefolate calcium
   Subjects: Normal healthy males and females, general population
   Additional Comments: Please see above in Study 1.

Analytes to measure (in appropriate biological fluid): Drospirenone, ethinyl estradiol in plasma, and L-5-methytetrahydrofolate (L-5-MTHF) in plasma or serum for combination tablets. L-5-MTHF for the single component tablet.

Please provide baseline correction for endogenous L-5-MTHF in the analysis. Please measure baseline L-5-MTHF levels at -0.5 and 0 hours predose, following a fasting period of at least 10 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): Drospirenone, ethinyl estradiol in plasma and baseline-adjusted L-5-MTHF in plasma or serum.

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

Cross-referencing and Waiver request of in-vivo testing: Package of Drospirenone/Ethinyl Estradiol/ Levomefolate Calcium Tablets, 3 mg/0.02 mg/0.451 mg, and Levomefolate Calcium Tablets, 0.451 mg, based on (i) cross-referencing of acceptable studies for the Drospirenone/Ethinyl Estradiol/Levomefolate Calcium Tablets, 3 mg/0.03 mg/0.451 mg, and an acceptable fasting study for Levomefolate Calcium Tablets, 0.451 mg, from a separate sister application, (ii) acceptable dissolution testing across all strengths of the combination and single-component tablets, and (iii) proportional similarity in the formulations between the two combination strengths, 3 mg/0.02 mg/0.451 mg and 3 mg/0.03 mg/0.451 mg of Drospirenone/Ethinyl Estradiol/ Levomefolate Calcium Tablets, and sameness in the formulation of Levomefolate Calcium Tablets, 0.451 mg between two applications.

If only the lower strength package, 3 mg/0.02 mg/0.451 mg Drospirenone/Ethinyl Estradiol and Levomefolate Calcium Tablets, with 0.451 mg Levomefolate Calcium Tablets, is to be marketed first, then the fasting and fed studies should be conducted on this lower combination strength, comparing it with the equal strength of the reference product. In addition, the fasting study should be conducted on the Levomefolate Calcium Tablets, 0.451 mg. However, if you decide to market the higher strength package, Drospirenone/Ethinyl Estradiol and Levomefolate Calcium, 3 mg/0.03 mg/0.451 mg, and Levomefolate Calcium Tablets, 0.451 mg, after the in-vivo studies of the lower strength package have been conducted, an additional fasting study will be requested for the higher combination strength.

Please note that if different NDAs of the package of Drospirenone/Ethinyl Estradiol and Levomefolate Calcium Tablets, 3 mg/0.02 mg/0.451 mg, and Levomefolate Calcium Tablets, 0.451 mg and the package of Drospirenone/Ethinyl Estradiol and Levomefolate Calcium Tablets, 3 mg/0.03 mg/0.451 mg and Levomefolate Calcium Tablets, 0.451 mg are referenced, then separated applications must be submitted. Please refer to the Guidance for Industry, Variations in Drug Products that May Be Included in a Single ANDA location at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072892.pdf

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.