Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Drospirenone; Ethinyl Estradiol; Levomefolate Calcium

October 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredients: Drospirenone; Ethinyl estradiol; Levomefolate calcium

Dosage Form: Tablet

Route: Oral

Strengths: 3 mg; 0.02 mg; 0.451 mg, 3 mg; 0.03 mg; 0.451 mg, N/A; N/A; 0.451 mg

Recommended Studies: Two in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 3 mg; 0.03 mg; 0.451 mg
   Subjects: Healthy non-pregnant, non-lactating females
   Additional comments: To minimize folate intake, meals containing negligible amount of folate should be provided to subjects during the confinement period. Measure and report the total folate content of each meal provided during the study period.

2. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.451 mg tablet of levomefolate calcium
   Subjects: Healthy non-pregnant, non-lactating females
   Additional comments: See comments above

Analytes to measure: Drospirenone and ethinyl estradiol in plasma, and L-5-methytetrahydrofolate (L-5-MTHF) in plasma or serum

Provide baseline correction for endogenous L-5-MTHF in the analysis. Measure baseline L-5-MTHF concentrations at -0.5 and 0 hours predose, following a fasting period of at least 8 hours. The mean of the pre-dose concentrations should be used for the baseline adjustment of the post-dose concentrations. 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 C_{max} 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 an acceptable bioequivalence study for the drospirenone; ethinyl estradiol; levomefolate calcium tablets, 3 mg; 0.03 mg; 0.451 mg, and an acceptable bioequivalence 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 of 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 of 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; levomefolate calcium tablets, with 0.451 mg levomefolate calcium tablets, is to be marketed, then the fasting bioequivalence study should be conducted on this lower combination strength, comparing it with the equal strength of the reference listed drug (RLD). In addition, the fasting bioequivalence study should be conducted on the levomefolate calcium tablets, 0.451 mg. However, if applicants plan to market the higher strength package, drospirenone; ethinyl estradiol; 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 bioequivalence study may be requested for the higher combination strength.

Note that if different NDAs of the package of drospirenone; ethinyl estradiol; 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; 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. Refer to the most recent version of the Guidance for Industry on, *Variations in Drug Products that May Be Included in a Single ANDA.*[a]

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 RLD.[1] Specifications will be determined upon review of the abbreviated new drug application.

Document History: Recommended March 2012; Revised October 2024

Unique Agency Identifier: PSG_022532

[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[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.*