Contains Nonbinding Recommendations

Draft Guidance on Ethinyl Estradiol; Levonorgestrel

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 0.03 mg/0.15 mg of ethinyl estradiol and levonorgestrel
   Subjects: Healthy nonpregnant females, general population
   Additional Comments: None

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2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: 0.03 mg/0.15 mg of ethinyl estradiol and levonorgestrel
   Subjects: Healthy nonpregnant females, general population
   Additional Comments: None

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3. Type of study: Fasting (if applicable)
   Design: Single-dose, two-way crossover in vivo
   Strength: 0.01 mg tablet of ethinyl estradiol
   Subjects: Healthy non-pregnant females, general population
   Additional Comments: None

Analytes to measure (in appropriate biological fluid): Ethinyl estradiol and levonorgestrel in plasma for the combination tablets. Only ethinyl estradiol for the single component tablet.

Bioequivalence based on (90% CI): Ethinyl estradiol and levonorgestrel

Cross-referencing of in vivo bioequivalence testing:

1. When referencing different NDAs of Ethinyl Estradiol and Levonorgestrel Tablets (0.03 mg/0. 15 mg, 0.025 mg/0. 15 mg, and 0.02 mg/0. 15 mg; 0.03 mg/0. 15 mg; and 0.02 mg/0.1 mg) as designated in the RLD application number column, separate applications must be submitted. Please refer to the Guidance for Industry, *Variations in Drug Products that May Be Included in a Single ANDA* located

at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064995.htm

2. For applications containing the same strength (of Ethinyl Estradiol/Levonorgestrel Tablets or Ethinyl Estradiol Tablets) as that used in the bioequivalence studies but submitted in a separate ANDA, you may cross-reference based on (1) acceptable bioequivalence studies of this strength in another related ANDA, (2) acceptable in vitro dissolution testing of both formulations of the same strength, and (3) proportional similarity of the formulations of the same strength.

Waiver request of in vivo testing: For the lower strengths (0.025 mg/0.15 mg, 0.02 mg/0.15 mg, and 0.02 mg/0.1 mg Ethinyl Estradiol/Levonorgestrel) submitted in a separate ANDA, based on (1) acceptable fasting and fed bioequivalence studies on the 0.03 mg/0.15 mg strength in another related ANDA, (2) acceptable in vitro dissolution testing of all strengths, and (3) proportional similarity of the formulations across all strengths.

If only the low strength, 0.02 mg/0.1 mg Ethinyl Estradiol/Levonorgestrel (together with the 0.01 mg Ethinyl Estradiol strength), is to be marketed first, the fasting and fed studies should be conducted on the 0.02 mg/0.1 mg Ethinyl Estradiol/Levonorgestrel, and a fasting study should be conducted on the 0.01 mg Ethinyl Estradiol strength, comparing them with the respective equal strengths of the reference product. However, if the higher strength, 0.03 mg/0.15 mg Ethinyl Estradiol/Levonorgestrel is to be marketed at a later time after *the in vivo* studies of the 0.02 mg/0.1 mg Ethinyl Estradiol/Levonorgestrel and 0.01 mg Ethinyl Estradiol were conducted, an ***additional*** fasting study will be requested for the higher combination strength.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website 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 (ANDA).