Contains Nonbinding Recommendations

Draft Guidance on Ethinyl Estradiol; Norethindrone Acetate

Active ingredient: Ethinyl Estradiol; Norethindrone Acetate

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 0.030 mg/1.5 mg (28 day packet)
   Subjects: Healthy nonpregnant females, general population
   Additional Comments: Subjects should not be taking hormonal contraceptives

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2. Type of study: Fed
   Design: Single-dose, two-way, crossover *in-vivo*
   Strength: 0.030 mg/1.5 mg (28 day packet)
   Subjects: Healthy nonpregnant females, general population
   Additional comments: Please see comment above

Analytes to measure: Ethinyl Estradiol; Norethindrone in plasma

Bioequivalence based on (90% CI): Ethinyl Estradiol; Norethindrone

Waiver request of in-vivo testing: 0.02 mg/1 mg (28 day), 0.02/1 mg (24 day) and 0.02 mg/1 mg (21 day) based on (i) acceptable bioequivalence studies on the 0.030 mg/1.5 mg (28 day packet) strength, (ii) acceptable dissolution testing across all strengths, and (iii) proportional similarity in the formulations across all strengths.

Cross-referencing of in-vivo testing: For the same strength, 0.030 mg/1.5 mg (21 day packet), as that used in the bioequivalence studies but submitted in a separate ANDA, based on (i) acceptable bioequivalence studies of this strength in the separate ANDA, (ii) acceptable in- vitro dissolution testing of the formulations of the same strength, and (iii) sameness (except for the colorants) of the formulations of the same strength.

If only the lower strength, 0.02 mg/1 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 RLD. However, if the higher strength, 0.03 mg/1.5 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.

Please note that if different NDAs of the Ethinyl Estradiol and Norethindrone Acetate tablets 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.fds.giv/cder/guidance.

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.