

Contains Nonbinding Recommendations

Draft Guidance on Ethinyl Estradiol; Norgestimate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Randomized, single-dose, two-way crossover, *in-vivo*
Strength: 0.035 mg/0.25 mg Ethinyl Estradiol/Norgestimate
Subjects: Healthy nonpregnant females, general population.
Additional Comments:

2. Type of study: Fed
Design: Randomized, single-dose, two-way crossover, *in-vivo*
Strength: 0.035 mg/0.25 mg Ethinyl Estradiol/Norgestimate
Subjects: Healthy nonpregnant females, general population.
Additional Comments:

Analytes to measure (in appropriate biological fluid): Ethinyl Estradiol and 17-Desacetyl Norgestimate in plasma.

Please develop a method of adequate sensitivity to accurately measure ethinyl estradiol concentrations in plasma. However, if you find that it is not possible to accurately measure ethinyl estradiol plasma concentrations following administration of a single dosage unit, it is adequate to administer 2 tablets of the test or reference product. No more than two tablets should be administered due to safety concerns.

Bioequivalence based on (90% CI): Ethinyl Estradiol and 17-Desacetyl Norgestimate

Waiver request of in-vivo testing: 0.035 mg/0.215 mg, 0.035 mg/0.180 mg, 0.025 mg/0.25 mg, 0.025 mg/0.215 mg, and 0.025 mg/0.18 mg based on (i) adequate bioequivalence studies on the 0.035 mg/0.25 mg strength, (ii) proportional similarity in the formulations of all strengths, and (iii) adequate *in vitro* dissolution testing of all strengths.

Cross-referencing of *in-vivo* testing:

Please note that Ethinyl Estradiol and Norgestimate Tablets, 0.035 mg/0.25 mg and 0.035 mg/0.215 mg, 0.035 mg/0.18 mg, and 0.025 mg/0.18 mg, 0.25/0.215 mg and 0.25/0.25 mg, are the subject of three separate reference products (NDAs 19-653, 19-697 and 21-241). Three separate applications must be submitted comparing to the appropriate reference products. An applicant may request a waiver of in vivo bioequivalence testing for generic of these RLDs provided that it (1) submits an ANDA containing acceptable in vivo studies on the 0.035 mg/0.25 mg strength; (2) cross-references the ANDA for the 0.035 mg/0.25 mg strength; and (3) meets the criteria of 21 CFR § 320.22(d)(2). 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>

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.