Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Estradiol; Norethindrone Acetate; Relugolix

December 2025

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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Active Ingredients: Estradiol; Norethindrone acetate; Relugolix

Dosage Form: Tablet

Route: Oral

Strength: 1 mg; 0.5 mg; 40 mg

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1 mg; 0.5 mg; 40 mg
   Subjects: Healthy postmenopausal females
   Additional comments:
   - Exclude subjects with a history or family history of hormonally-sensitive malignancies. Exclude subjects with history of or risk factors for thromboembolic disorders and vascular events.
   - Applicants may consider using a reference-scaled average bioequivalence approach for relugolix. If using this approach, provide evidence of high variability in the pharmacokinetic parameters (i.e., within-subject variability ≥30%) for the reference product. For detailed information on this approach, refer to the most recent version of the FDA guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*[a] Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of relugolix. Alternatively, a parallel study design may be considered.

Analytes to measure: Unconjugated estradiol, norethindrone, and relugolix in plasma

Measure baseline unconjugated estradiol at -1, -0.5, and 0 hours before dosing. The mean of the pre-dose unconjugated estradiol should be used for the baseline correction. Pharmacokinetics and statistical analyses should be performed on both baseline uncorrected and baseline corrected data.

Bioequivalence based on (90% CI): Baseline-corrected unconjugated estradiol, norethindrone, and relugolix

Waiver request of in vivo testing: Not applicable

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 the test product and reference listed drug (RLD).[1] Specifications will be determined upon evaluation of the abbreviated new drug application.

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Unique Agency Identifier: PSG_214846

[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 guidance for industry *Referencing Approved Drug Products in ANDA Submissions*.