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Draft – Not for Implementation

Draft Guidance on Elagolix Sodium, Estradiol, Norethindrone Acetate; Elagolix Sodium

February 2024

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Active Ingredients:	Elagolix sodium, Estradiol, Norethindrone acetate; Elagolix sodium
Dosage Form:	Capsule
Route:	Oral
Strength:	EQ 300 mg Base, 1 mg, 0.5 mg; EQ 300 mg Base
Recommended Studies:	Two options: (1) two in vivo bioequivalence studies with pharmacokinetic endpoints on elagolix sodium, estradiol, norethindrone acetate capsule, or (2) two in vivo bioequivalence studies with pharmacokinetic endpoints on elagolix sodium capsule

I. Option 1: Two in vivo bioequivalence studies with pharmacokinetic endpoints on elagolix sodium, estradiol, norethindrone acetate capsule

This drug product is co-packaged with the elagolix sodium, estradiol, norethindrone acetate capsule and elagolix sodium capsule. Bioequivalence of both elagolix sodium, estradiol, norethindrone acetate capsule and elagolix sodium capsule may be established if the following three conditions are met: (i) demonstrating bioequivalence on elagolix, estradiol, and norethindrone using a fixed dose combination of elagolix sodium, estradiol, and norethindrone acetate capsule in two in vivo bioequivalence studies under fasting and fed conditions, (ii) demonstrating elagolix sodium formulations in both capsules are identical (e.g., same formulation composition, manufacturing process and process controls, and same quality standards), and (iii) demonstrating comparable in vitro dissolution testing of the elagolix sodium component from both capsules.

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 300 mg Base, 1 mg, 0.5 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. Exclude subjects with abnormal liver function tests.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 300 mg Base, 1 mg, 0.5 mg
   Subjects: Healthy postmenopausal females
   Additional comments: See comments above.

Analytes to measure: Elagolix, unconjugated estradiol, unconjugated estrone, total estrone and norethindrone in plasma

Measure baseline unconjugated estradiol, unconjugated estrone and total estrone concentrations at -1, -0.5, and 0 hours before dosing. The mean of the pre-dose unconjugated estradiol, unconjugated estrone and total estrone concentrations should be used for the baseline correction.

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

Statistical analysis should be performed on data both with and without baseline adjustment. Provide the data for unconjugated estrone and total estrone as supportive evidence of comparable therapeutic outcome. The following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for each component of this co-packaged 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 and reference products. Specifications will be determined upon evaluation of the abbreviated new drug application (ANDA).

II. Option 2: Two in vivo bioequivalence studies with pharmacokinetic endpoints on elagolix sodium capsule

If reference is made to an approved drug product or an ANDA that is under review for the estradiol; norethindrone acetate 1 mg; 0.5 mg tablet, bioequivalence of both elagolix sodium, estradiol, norethindrone acetate capsule and elagolix sodium capsule may be established if the following four conditions are met: (i) demonstrating bioequivalence on elagolix using an elagolix sodium capsule in two in vivo bioequivalence studies under fasting and fed conditions, (ii) demonstrating elagolix sodium formulations in both capsules are identical (e.g., same formulation composition, manufacturing process and process controls, and same quality standards), (iii) demonstrating comparable in vitro dissolution testing of the elagolix sodium component from both capsules, and (iv) acceptable in vitro dissolution testing of estradiol and norethindrone acetate by comparing the estradiol; norethindrone acetate tablet to the elagolix sodium, estradiol, norethindrone acetate capsule.

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 300 mg Base
   Subjects: Healthy non-pregnant, non-lactating premenopausal females
   Additional comment: Exclude subjects with abnormal liver function tests.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 300 mg Base
   Subjects: Healthy non-pregnant, non-lactating premenopausal females
   Additional comment: See comment above.

Analyte to measure: Elagolix in plasma

Bioequivalence based on (90% CI): Elagolix

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for each component of this co-packaged 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 and reference products. Specifications will be determined upon evaluation of the ANDA.

Document History: Recommended February 2024

Unique Agency Identifier: PSG_213388