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Draft Guidance on Ethinyl Estradiol; Norgestrel

October 2024

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Active Ingredients: Ethinyl estradiol; Norgestrel

Dosage Form: Tablet

Route: Oral-21, Oral-28

Strengths: 0.03 mg; 0.3 mg, 0.05 mg; 0.5 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: 0.05 mg; 0.5 mg
   Subjects: Healthy non-pregnant, non-lactating females
   Additional comments: None

Analytes to measure: Ethinyl estradiol and norgestrel in plasma

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

Waiver request of in vivo testing: Not applicable

Cross-referencing of in vivo testing: For the lower strength, 0.03 mg; 0.3 mg submitted in a separate abbreviated new drug application (ANDA), based on (i) acceptable bioequivalence study of the 0.05 mg; 0.5 mg strength from a separate but related ANDA, (ii) cross-referencing of the studies above in the separate ANDA of the 0.05 mg; 0.5 mg strength (iii) acceptable in vitro dissolution testing of both strengths, and (iv) proportional similarity of the formulations between both strengths

If only the lower strength, 0.03 mg; 0.3 mg, 21-day regimen or 28-day regimen, is to be marketed first, the bioequivalence study should be conducted on this lower strength, comparing it with the equal strength of the reference listed drug (RLD) of the same bundle (linked to the current guidance). In such case, if later the higher strength, 0.05 mg; 0.5 mg 21 or 28-day regimen is to be marketed, an additional fasting bioequivalence study will be requested for this higher strength of 21 or 28-day regimen, without cross-referencing of the studies of the lower strength.

Note that if different NDA/ANDAs of ethinyl estradiol and norgestrel tablets, 0.03 mg; 0.3 mg and 0.05 mg; 0.5 mg are referenced, separate applications must be submitted. Refer to the most recent version of the FDA guidance for industry on *Variations in Drug Products that May Be Included in a Single ANDA*.[a]

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 all strengths of the test product and RLD.[1] Specifications will be determined upon review of the abbreviated new drug application.

Document History: Recommended October 2009; Revised October 2024

Unique Agency Identifier: PSG_016672

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