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Draft Guidance on Ethinyl Estradiol; Ethynodiol Diacetate

October 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form: Tablet

Route: Oral-21, Oral-28

Strengths: 0.05 mg; 1 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; 1 mg
   Subjects: Healthy non-pregnant, non-lactating females
   Additional comments: None

Analytes to measure: Ethinyl estradiol and norethindrone (active metabolite of ethynodiol diacetate)

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

Cross-referencing of in vivo testing: For the lower strength, 0.035 mg; 1 mg submitted in a separate abbreviated new drug application (ANDA), based on (i) acceptable bioequivalence study of the 0.05 mg; 1 mg strength from a separate but related ANDA, (ii) cross-referencing of the study above in the separate ANDA of the 0.035 mg; 1 mg strength (iii) acceptable in vitro dissolution testing of both strengths, and (iv) proportional similarity of the formulations between two strengths.

If only the lower strength, 0.035 mg; 1 mg (21 day or 28 day regimen), is to be marketed first, the fasting study should be conducted on this lower strength, comparing it with the equal strength of the reference listed drug (RLD) of the same bundle. In such case, if later the higher strength, 0.05 mg; 1 mg is to be marketed, an additional fasting study will be requested for this higher strength without cross-referencing of the studies of the lower strength.

Note that if different new drug applications/ANDAs of ethinyl estradiol and ethynodiol diacetate tablets, 0.035 mg; 1 mg and 0.05 mg; 1 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 both strengths of the test product and reference listed drug (RLD).[1] Specifications will be determined upon review of the ANDA.

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[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.*