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Draft Guidance on Levonorgestrel

October 2024

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Active Ingredient: Levonorgestrel

Dosage Form: Tablet

Route: Oral

Strengths: 0.75 mg, 1.5 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: 1.5 mg
Subjects: Healthy non-pregnant, non-lactating females
Additional comments: None

Analyte to measure: Levonorgestrel in plasma

Bioequivalence based on (90% CI): Levonorgestrel

Waiver request of in vivo testing: 0.75 mg strength based on (i) acceptable bioequivalence study on the 1.5 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths

Since levonorgestrel tablets, 1.5 mg and 0.75 mg are the subject of two separate applications, two separate abbreviated new drug applications (ANDAs) must be submitted. A waiver of in vivo bioequivalence testing of the 0.75 mg strength may be requested if the criteria are met. The in vivo bioequivalence studies conducted on 1.5 mg strength may be cross-referenced, along with the in vivo waiver request. 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

If only the lower strength, 0.75 mg, is to be marketed first, conduct the studies recommended above comparing the test 0.75 mg strength to the corresponding strength of the reference product. However, if the higher strength, 1.5 mg, is to be marketed at a later time after the in vivo studies on the 0.75 mg strength were conducted, an additional fasting study will be requested for the 1.5 mg strength.

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*.