

**Draft Guidance on Ribociclib Succinate and Letrozole
(From the Ribociclib Succinate, Letrozole Co-Packaged Tablets)**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Ribociclib succinate

Dosage Form; Route: Tablet; Oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 200 mg BASE
Subjects: Females of non-child bearing potential, general population
Additional comments: The tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). Due to potential for impairment of male fertility and embryo-fetal toxicity, studies should not be conducted in males and females of child bearing potential. Also consider using a parallel study design due to ribociclib long half-life. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of gastrointestinal transit of the drug product and absorption of the drug substance. Collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak concentration C_{max} and time to reach peak concentration T_{max} .

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2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: EQ 200 mg BASE
Subjects: Females of non-child bearing potential, general population
Additional comments: See above
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Active Ingredient: Letrozole

Dosage Form; Route: Tablet; Oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 2.5 mg

Subjects: Females of non-child bearing potential, general population

Additional comments: Consider using a parallel study design due to letrozole long half-life. For long half-life drug products with low intra-subject variability in distribution and clearance, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or AUC_{0-∞}. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of gastrointestinal transit of the drug product and absorption of the drug substance. Collect sufficient blood samples in the bioequivalence studies to adequately characterize C_{max} and T_{max}.

2. Type of study: Fed

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 2.5 mg

Subjects: Females of non-child bearing potential, general population

Additional comments: See above

Analytes to measure (in appropriate biological fluid): Ribociclib and letrozole in plasma

Bioequivalence based on (90% CI): Ribociclib and letrozole

Waiver request of in vivo testing: Not applicable

Since this product is co-packaged with ribociclib succinate tablet and letrozole tablet, ANDA applicants may conduct only two bioequivalence studies under both fasting and fed conditions by co-administration of this co-packaged product. Both ribociclib and letrozole should be measured to demonstrate bioequivalence in these studies.

If ANDA applicants have approved ANDA for individual components of this co-packaged product, the approved ANDA may be cross-referenced.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).