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Draft Guidance on Nirmatrelvir; Ritonavir

August 2024

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Active Ingredients: Nirmatrelvir; Ritonavir

Dosage Form: Tablet; Tablet

Route: Oral

Strengths: 150 mg; 100 mg

Recommended Studies: Two options: (1) two in vivo bioequivalence studies with pharmacokinetic endpoints on nirmatrelvir and ritonavir, or (2) one in vivo bioequivalence study with pharmacokinetic endpoints on nirmatrelvir

I. Option 1: Two in vivo bioequivalence studies with pharmacokinetic endpoints on nirmatrelvir and ritonavir

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strengths: 150 mg; 100 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: The reference list drug (RLD) is co-packaged with nirmatrelvir tablets and ritonavir tablets. Conduct the study by co-administering nirmatrelvir tablet and ritonavir tablet as ritonavir is used as a pharmacokinetic enhancer.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strengths: 150 mg; 100 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

Analytes to measure: Nirmatrelvir and ritonavir in plasma

Bioequivalence based on (90% CI): Nirmatrelvir and ritonavir

Waiver request of in vivo testing: Not applicable

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 units each of the test and reference listed drug products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints on nirmatrelvir

This option is applicable only if applicants cross-reference an approved new drug application or ANDA of ritonavir tablet for their co-packaged ANDA.

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strengths: 150 mg; 100 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Conduct the study by co-administering nirmatrelvir tablet and ritonavir tablet as ritonavir is used as a pharmacokinetic enhancer. It is acceptable to demonstrate bioequivalence based on nirmatrelvir without measurement of ritonavir.

Analyte to measure: Nirmatrelvir in plasma

Bioequivalence based on (90% CI): Nirmatrelvir

Waiver request of in vivo testing: Not applicable

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 units each of the test and reference listed drug products using nirmatrelvir tablets. Specifications will be determined upon review of the ANDA.

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