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Draft Guidance on Ledipasvir; Sofosbuvir

May 2021

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In September 2015, FDA issued a draft product-specific guidance for industry on generic ledipasvir; sofosbuvir. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredients: Ledipasvir; Sofosbuvir

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: 90 mg; 400 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: Measure hepatitis B surface antigen and hepatitis B core antibody and exclude subjects with evidence of current or prior hepatitis B virus infection. Due to the potential risk of serious symptomatic bradycardia, exclude subjects who are taking amiodarone. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of ledipasvir. Alternatively, a parallel study design may be considered.

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 90 mg; 400 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.

Analytes to measure: Ledipasvir and sofosbuvir in plasma

Bioequivalence based on (90% CI): Ledipasvir and sofosbuvir

Waiver request of in vivo testing: 45 mg; 200 mg based on (i) acceptable bioequivalence studies on the 90 mg; 400 mg strength, (ii) proportional similarity of the formulations between both strengths, and (iii) acceptable in vitro dissolution testing of both strengths.

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 and reference products. Specifications will be determined upon review of the abbreviated new drug application.

Revision History: Recommended September 2015; Revised May 2021

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