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Draft – Not for Implementation

Draft Guidance on Ivacaftor; Ivacaftor, Tezacaftor

March 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

In February 2019, FDA issued a final product-specific guidance for industry on generic ivacaftor; ivacaftor, tezacaftor. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Ivacaftor

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: 150 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 150 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: None

Analyte to measure: Ivacaftor in plasma

Bioequivalence based on (90% CI): Ivacaftor

Waiver request of in vivo testing: 75 mg based on (i) acceptable bioequivalence studies on the 150 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between both strengths.

If an abbreviated new drug application (ANDA) applicant has an approved ANDA for the single entity of 150 mg ivacaftor tablet, the applicant may cross reference its approved ANDA for this co-packaged product. In addition, the applicant should follow the above waiver criteria for 75 mg.

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.

Active Ingredient: Ivacaftor; Tezacaftor

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: 150 mg; 100 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 150 mg; 100 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: None

Analytes to measure: Ivacaftor and tezacaftor in plasma

Bioequivalence based on (90% CI): Ivacaftor and tezacaftor

Waiver request of in vivo testing: 75 mg; 50 mg strength based on (i) acceptable bioequivalence studies on the 150 mg; 100 mg strength, (ii) acceptable in vitro dissolution testing of both strengths, and (iii) proportional similarity of the formulations between 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 February 2019; Revised March 2021

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