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Draft – Not for Implementation

Draft Guidance on Pirtobrutinib

May 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Pirtobrutinib

Dosage Form: Tablet

Route: Oral

Strengths: 50 mg, 100 mg

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 100 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude subjects with abnormal blood counts. Exclude subjects with abnormal electrocardiograms or risk factors for cardiac arrhythmias. Females of reproductive potential should use non-hormonal contraception during the study and continue to use effective contraception for one week after the last dose.

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

Analyte to measure: Pirtobrutinib in plasma

Bioequivalence based on (90% CI): Pirtobrutinib

Waiver request of in vivo testing: 50 mg strength based on (i) acceptable bioequivalence studies on the 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 each of both strengths of the test and reference products. Specifications will be determined upon evaluation of the abbreviated new drug application.

In addition to the method above, the application should include dissolution profiles for 12 dosage units each of both strengths of the test and reference listed drug products generated using U.S. Pharmacopeia Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm, across at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer). If necessary, agitation speeds may be adjusted accordingly. The addition of a minimal amount of surfactant is permissible if required. The profiles should include early sampling times of 5, 10, 15, and 30 minutes and continue at every 15 minutes intervals until at least 80% of the drug is released.

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