Contains Nonbinding Recommendations

Draft Guidance on Ibrutinib

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: 560 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: 1) Due to the embryo-fetal toxicity of ibrutinib, females should avoid pregnancy and use effective method of contraception during the study and continue through one month following the last dose of ibrutinib. Males should use effective method of contraception and for at least one month following the last dose of ibrutinib. 2) Applicants may consider using a reference-scaled average bioequivalence approach for ibrutinib. If using this approach, provide evidence in the studies of high variability in the bioequivalence parameters of area under the plasma concentration time curve and/or peak concentration (i.e., within-subject variability ≥ 30%). For detailed information on this approach, refer to the guidance for Progesterone Oral Capsules.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 560 mg
   Subjects: Males and non-pregnant, non-lactating females, general population
   Additional comments: See comments above

Analyte to measure (in appropriate biological fluid): Ibrutinib in plasma

Bioequivalence based on (90% CI): Ibrutinib

Waiver request of in vivo testing: 140 mg, 280 mg, and 420 mg based on (i) acceptable bioequivalence studies on the 560 mg strength, (ii) proportionally similar formulation across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths

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.