

Draft Guidance on Lorlatinib

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Study: One study

1. Type of study: Steady-state
Design: Multiple-dose, two-way crossover in vivo
Strength: 100 mg
Subjects: Patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer whose disease has progressed on one or more ALK inhibitor therapy for metastatic disease already receiving stable dose of Lorlatinib Tablets
Additional comments: Submission of a Bio Investigational New Drug Application (BioIND) is required prior to the conduct of a bioequivalence study for a cytotoxic drug product such as lorlatinib (see 21CFR § 320.31).

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

Bioequivalence based on (90% CI): Lorlatinib

In the evaluation of the steady-state BE study, the following PK data should be submitted for lorlatinib: $AUC_{0-\tau}$, and C_{maxSS} . In addition, report C_{minSS} (concentration at the end of a dosing interval), C_{avSS} (average concentration during a dosing interval), degree of fluctuation [$(C_{max} - C_{min})/C_{avSS}$], swing [$(C_{maxSS} - C_{minSS})/C_{minSS}$], and T_{max} .

Waiver request of in vivo testing: 25 mg strength based on (i) acceptable bioequivalence study on the 100 mg strength, (ii) proportional similarity of the formulations across two strengths, and (iii) acceptable in vitro dissolution testing of two 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 two strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.