

Draft Guidance on Ponatinib Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Multiple-dose, two-way crossover pharmacokinetic (PK) steady-state study in patients

1. Type of study: PK steady-state
Design: Multiple-dose, two-way crossover steady-state PK study in patients
Strength: 45 mg
Study subjects: The study should be conducted in adult patients with: 1) T315I-positive chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) and/or 2) chronic-phase, accelerated-phase, or blast-phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated

Additional comments:

- 1) Attainment of steady state should be based on at least three consecutive trough levels
- 2) Blood sampling for bioequivalence should consist of appropriate sampling times over a 24-hour period following attainment of steady state
- 3) Study subjects and their partners should practice abstinence or adequate contraception during the study and for at least one week after the last ponatinib dose
- 4) Investigators should refer to the “Warnings, Precautions, Contraindications, and Adverse Reactions” in the FDA-approved labeling and follow the directions closely
- 5) The study should be designed around each patient’s existing ponatinib regimen
- 6) No changes in dose or regimen should be made for the purpose of the bioequivalence (BE) study

Analytes to measure (in appropriate biological fluid): Ponatinib in plasma

Bioequivalence based on (90% CI): Ponatinib

Waiver request of in vivo testing: 15 mg and 30 mg strengths based on:

- 1) Acceptable multiple-dose, steady-state PK BE study in patients on the 45 mg ponatinib tablet

- 2) Proportional similarity of formulations across all strengths
- 3) 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 (ANDA).