Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Avutometinib Potassium; Defactinib Hydrochloride

May 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form: Capsule; Tablet

Route: Oral

Strength: EQ 0.8 mg Base; EQ 200 mg Base

Reference Listed Drug: NDA 219616

Recommended Studies: Two in vivo bioequivalence study with pharmacokinetic endpoints

1. Class of study: Bioequivalence
   Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 0.8 mg Base (avutometinib potassium capsule)
   Dose: EQ 2.4 mg Base
   Subjects: Healthy females not of reproductive potential
   Safety recommendations:
   - Exclude subjects with a history of or any risk factors for serious retinopathy or retinal vein occlusion (e.g., uncontrolled glaucoma, history of hyperviscosity or hypercoagulability syndromes), or abnormal ophthalmic exam findings.
   - Subjects should be administered prophylactic medications (e.g., topical corticosteroid and systemic oral antibiotics).
   - Ensure that there is no drug-drug interaction between the prophylactic medications and avutometinib, and that the prophylactic medications do not interfere with the bioanalytical method used to analyze plasma concentrations of avutometinib.

- Subjects should be advised to limit sun exposure and use appropriate sun protection during the study to prevent dermatologic adverse reactions.

Study design recommendations:

- $AUC_{(0\text{-}72h)}$ may be used in place of $AUC_{(0\text{-}t)}$ for comparing the extent of absorption due to the avutometinib's long half-life. Ensure an adequate washout period between treatments in the crossover study.
- Alternatively, a parallel study design may be considered.

Analyte to measure: Avutometinib in plasma

Bioequivalence based on (90% CI): Avutometinib

2. Class of study: Bioequivalence
   Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 200 mg Base (defactinib hydrochloride tablet)
   Subjects: Healthy females not of reproductive potential

Analyte to measure: Defactinib in plasma

Bioequivalence based on (90% CI): Defactinib

Waiver request of in vivo testing of additional strength: Not applicable

Dissolution: Dissolution test(s) should be included for quality control. Provide a dissolution method development report for the test product containing information and data that demonstrate appropriateness of the selected dissolution method[1] and sampling times, such as the discriminating ability to detect changes in critical quality attributes that could potentially impact drug product performance.

Document History: Recommended May 2026

[1] Applicant-developed, United States Pharmacopeia drug product monograph or Dissolution Methods database, https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm