

## Draft Guidance on Axitinib

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Axitinib

**Form/Route:** Tablet/Oral

**Recommended studies:** 2 studies

1. Type of study: Fasting

Design: Single dose, two way crossover, in vivo

Strength: 5 mg

Subjects: Healthy males and non-pregnant females, general population.

Additional Comments: Adhere to the following additional comments regarding the study population, exclusion criteria, safety monitoring, stopping rules and informed consent:

- i. Recommended study population: healthy subjects  $\geq 18$  years of age with no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate (PR) measurement, 12-lead electrocardiogram (ECG) and clinical laboratory tests.
- ii. We recommend the following exclusion criteria:
  - a. Age  $< 18$  years
  - b. Pregnant or breastfeeding women
  - c. Women of childbearing potential
  - d. Individuals with hepatic, thyroid, or renal dysfunction
  - e. Current use or anticipated need for drugs with known or suspected interactions with axitinib
  - f. Subjects with hypertension or cardiovascular risk factors
  - g. Subjects with a history of gastrointestinal bleeding
- iii. We recommend the following safety monitoring (prior to dosing and after each dosing period) during the BE trial: pregnancy test for women, liver function tests, thyroid function tests, electrocardiogram, urinalysis, and blood pressure. In addition, males and their female partners need to practice adequate contraception for at least two weeks after the last dose of axitinib.
- iv. We recommend the following stopping rules: occurrence of two or more adverse events of  $>$  Grade 2 (Common Terminology Criteria for Adverse Events (CTCAE) or WHO Toxicity Criteria), any occurrence of  $>$  CTCAE Grade 3

adverse events, or any occurrence of a serious adverse event (SAE) possibly related to the study drug.

- v. FDA recommends that the Informed Consent should state that axitinib caused birth defects in animals and that the potential for axitinib to cause malignancies is unknown. Based on input from the FDA/Office of Hematology and Oncology Products (OHOP), FDA/Division of Clinical Review (DCR) also recommends including specific information on carcinogenicity and teratogenicity into the informed consent document.

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2. Type of study: Fed

Design: Single dose, two way crossover, in vivo

Strength: 5 mg

Subjects: Healthy males and non-pregnant females, general population.

Additional Comments: Same as the fasting study.

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**Analytes to measure (in appropriate biological fluid):** Axitinib in plasma

**Bioequivalence based on (90% CI):** Axitinib

**Waiver request of in vivo testing:** 1 mg tablet, based on (i) acceptable bioequivalence studies on the 5 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

**Dissolution test method and sampling times:**

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please 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 application.