Contains Nonbinding Recommendations

Draft Guidance on Pazopanib Hydrochloride

Active ingredient: Pazopanib HCl

Form/Route: Tablet/Oral

Recommended studies: 1 study

Type of study: Steady-state
Design: Two-period, two-treatment, fasting (at least one hr before or 2 hrs after a meal) parallel OR crossover
Strength: EQ 200 mg base (Dose: 4 × EQ 200 mg base tablets; currently, only the EQ 200 mg base strength tablet is marketed.)
Subjects: Advanced renal cell carcinoma patients for whom pazopanib is indicated, who are already receiving Pazopanib HCl tablets in standard therapy, and who are tolerating a stable dosing regimen of 800 mg/day (4 × 200 mg). Females should not be pregnant.
Additional comments: Submission of an Investigational New Drug Application (IND) is required prior to conducting a bioequivalence study for a cytotoxic drug product such as Pazopanib Hydrochloride (see 21 C.F.R § 320.31). Specific recommendations are provided below.

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

Bioequivalence based on (90% CI): Pazopanib

Waiver request of in-vivo testing: Not Applicable

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 drug 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.

Additional comments regarding the Bioequivalence (BE) study with Pharmacokinetic (PK) endpoints:

1. Recommend the following Inclusion Criteria:
   - Patients with disease confirmation of renal cell carcinoma.
   - Age > 18 years.
   - Normal organ and marrow function.
   - No significant medical comorbidities or intercurrent illnesses that could limit compliance with study medications or increase the risk of treatment-related toxicities.

- Women of childbearing potential are using adequate contraceptive methods. These contraceptive methods should be used during treatment and for at least one week after treatment discontinuation.

2. Recommend the following Exclusion Criteria:
   - Pregnant or lactating.
   - ECOG Performance Status of > 2.
   - Hepatic or renal impairment.
   - Hypokalemia, hypomagnesemia, long QT syndrome, or a history of cardiac disease.
   - Receiving any medications or substances that are strong inhibitors or inducers of the CYP450 enzyme. *Please see http://medicine.iupui.edu/flockhart for a list of inhibitors and/or inducers.*
   - Receiving any drugs known to prolong the QT interval within 4 weeks prior to study or during the study.

3. The study should be conducted in all patients using the same dosage strength tablet even when the patients are on different doses. If a patient's current dose cannot be given using multiples of the dosage strength being studied then that patient must be excluded from the study.

4. Each dose of the drug should be taken orally without food (at least 1 hr before or 2 hours after a meal).

5. Dosing on each treatment should continue for a sufficient time to allow achievement of pharmacokinetic steady-state on the test and reference treatments, hence for four to five half-lives prior to bioequivalence study plasma sampling. Similarly, sufficient time for re-equilibration should be allowed for a crossover treatment. Washout between treatment periods is not recommended or necessary.

6. All patients should be immediately switched back to the previously used product at the completion of the study.

7. Employ the standard baseline and periodic monitoring criteria used in clinical studies enrolling cancer patients [e.g., physical exam, vital signs, assessment of toxicities, serum chemistry, CBCs, performance status, and tumor assessments].

8. Obtain electrocardiograms, electrolytes (e.g., at a minimum calcium, magnesium, potassium), and serum pregnancy testing (in women of childbearing potential) at baseline and weekly during the study. Obtain serum liver test (ALT, AST, and bilirubin), urinalysis, and thyroid function testing at baseline and every 4 weeks during the study.

9. FDA recommends that the informed consent document include a statement clearly informing patients of the potential risks related to receiving a pazopanib product not previously tested for bioequivalence. This information should include a discussion of the potential risks related to administration of a subtherapeutic (e.g., lack of efficacy) and supratherapeutic pazopanib drug product (e.g., increased toxicity).