Contains Nonbinding Recommendations

Draft Guidance on Regorafenib

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 the 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: Regorafenib

Dosage Form; Route: Tablet; oral

Recommended Studies: Pharmacokinetic multiple-dose, two-treatment, steady-state, crossover study in patients

1. Type of study: Pharmacokinetic endpoint steady-state
   Design: Multiple-dose, two-way crossover using cancer patients
   Strength: 40 mg tablet (dose=4x40 mg i.e.160 mg* per day)
   Subjects: The study should be conducted in patients with 1) Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy, or 2) Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.
   Additional comments: 1) Attainment of steady state should be confirmed with at least 3 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) Females should practice abstention or contraception during the study. Investigators should refer to Warnings, Precautions, Contraindications, and Adverse Reactions in the FDA approved labeling and follow the directions closely. 4) Women of child-bearing potential should be advised to use an effective method of contraception while using regorafenib and for up to 8 weeks after ending the treatment. 5) Design the study around each patient’s existing regorafenib regimen. 6) No changes in dose or regimen should be made for the purpose of the bioequivalence study.

   ***The label-recommended dosing regimen is 160 mg oral once daily for the first 21 days of each 28-day treatment cycle.**

Analytes to measure (in appropriate biological fluid): Regorafenib and M2 metabolite in plasma

Submit the metabolic data as supportive evidence of comparable therapeutic outcome. For the metabolites, submit the following data: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Bioequivalence based on (90% CI): Regorafenib

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website 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).