Contains Nonbinding Recommendations

Draft Guidance on Tipiracil Hydrochloride; Trifluridine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Study: One study

1. Type of study: Steady-state
   Design: Multiple-dose, two-way crossover, fed, in vivo
   Strengths: EQ 6.14 mg Base, Tipiracil/15 mg Trifluridine; EQ 8.19 mg Base, Tipiracil/20 mg Trifluridine
   Subjects: Metastatic colorectal cancer patients 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
   Additional comments: 1) Attainment of steady state should be confirmed with at least 3 consecutive trough measurements; 2) Blood sampling for bioequivalence should consist of appropriate sampling times over a 12-hour period following attainment of steady state; 3) Females should not be pregnant or lactating, and if possible, should practice abstention or contraception during the study; 4) Design the study around each patient's existing Trifluridine/Tipiracil regimen; 5) No changes in dose or regimen should be made for the purpose of the bioequivalence study; 6) Submission of a Bio Investigational New Drug Application (BioIND) is required prior to the conduct of a bioequivalence study for a cytotoxic drug product such as tipiracil hydrochloride/trifluridine tablets (refer 21CFR § 320.31); 7) Applicants may consider using a reference-scaled average bioequivalence approach. If using this approach, provide evidence in the studies of high variability in the bioequivalence parameters of area under the plasma concentration time curve and/or peak concentration (i.e., within-subject variability ≥ 30%). For detailed information on this approach, refer to the guidance for Progesterone Oral Capsules.

Analytes to measure (in appropriate biological fluid): Trifluridine and tipiracil in plasma

Bioequivalence based on (90% CI): Trifluridine and tipiracil

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 the two strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.