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Draft Guidance on Tipiracil Hydrochloride; Trifluridine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: One study

1. Type of study: Bioequivalence study with pharmacokinetic endpoints under steady state

   Design: Multiple-dose, two-way crossover, fed, in vivo

   Strength: EQ 6.14 mg Tipiracil Base/15 mg Trifluridine; EQ 8.19 mg Tipiracil Base/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 levels. 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. Investigators should refer to Warnings, Precautions, Contraindications, and Adverse Reactions in the FDA approved labeling and follow the directions closely. 4) Collect sufficient blood samples in the bioequivalence studies to adequately characterize the maximum concentration (Cmax) and time to reach maximum concentration (tmax). 5) Design the study around each patient's existing Trifluridine/Tipiracil regimen. 6) No changes in dose or regimen should be made for the purpose of the bioequivalence study.

Analytes to measure (in appropriate biological fluid): Trifluridine, Tipiracil, and 5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione 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 C_{max}.

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/. 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 abbreviated new drug application (ANDA).