Contains Nonbinding Recommendations

Draft Guidance on Cobimetinib Fumarate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Cobimetinib fumarate

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 20 mg Base
   Subjects: Healthy males and females (non-pregnant and non-lactating), general population
   Additional Comments:
   - All the warnings specified in cobimetinib labeling should be followed and appropriately incorporated in the bioequivalence (BE) study design and informed consent. Females should not be pregnant or lactating, and the pregnancy status of females of reproductive potential should be verified prior to initiating therapy. If applicable, females should practice abstinence or contraception during and two weeks after the study.
   - Cobimetinib has a long terminal elimination half-life (>24 hours); therefore adequate washout periods should be ensured between treatments in the crossover studies. A parallel study design may also be considered due to its long half-life. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of gastrointestinal transit of the drug product and absorption of the drug substance. For long half-life drug products that demonstrate low intra-subject variability in distribution and clearance, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or $AUC_{0-\infty}$. Sufficient blood samples should be collected in the BE studies to adequately characterize the peak concentration (C_{max}) and time to reach peak concentration (T_{max}).

2. Type of study: Fed
   Design: Single-dose, two-way crossover *in vivo*
   Strength: EQ 20 mg Base
   Subjects: Healthy males and females (non-pregnant and non-lactating), general population
   Additional comments: See comments above.

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

Bioequivalence based on (90% CI): Cobimetinib

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 Web site, 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).