Contains Nonbinding Recommendations

Draft Guidance on Cabozantinib S-Malate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Capsule; oral

Recommended Studies: One study

1. Type of Study: Steady state
   Design: Two-treatment, two-period, crossover or parallel in vivo study with pharmacokinetic endpoints under fasted conditions
   Strength (Dose): EQ 20 mg Base (3 x EQ 20 mg Base, 5 x EQ 20 mg Base, or 7 x EQ 20 mg Base)
   Subjects: The study should be conducted in patients with progressive, metastatic medullary thyroid cancer (MTC) who have been stabilized on their dose
   Additional comments:
   a. Investigators should refer to the Warnings, Precautions, Contraindications, and Adverse Reactions in the FDA-approved labeling and follow the directions closely.
   b. Females should not be pregnant or lactating, and, if applicable, should practice abstention or contraception during the study and for four months after the final dose.
   c. Cabozantinib has a long half-life (approximately 55 hours). Therefore, blood sampling for bioequivalence analysis should allow sufficient time on the test and reference drug product in order to assure attainment of steady state; blood sampling should consist of appropriate sampling times over a 24 hour period following attainment of steady state. Additionally, attainment of steady state should be confirmed with at least three consecutive trough levels.

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

Bioequivalence based on (90% CI): Cabozantinib

Waiver request of in vivo testing: EQ 80 mg Base based on (i) acceptable bioequivalence studies on the EQ 20 mg Base strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing across all strengths.

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 of all strengths of the test and

reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).