Contains Nonbinding Recommendations

Draft Guidance on Osimertinib Mesylate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 80 mg Base
   Subjects: Males, general population.
   Additional Comments: Osimertinib has a long terminal elimination half-life (>24 hrs). For an oral immediate release drug product with a long elimination half-life (>24 hrs), applicants can conduct a single-dose, crossover study, provided an adequate washout period is used. If the crossover study is problematic, applicants should use a BE study with a parallel design. 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 (which usually occurs within approximately 2 to 3 days). You can use C_{max} and a suitably truncated AUC to characterize peak and total drug exposure, respectively. For drugs that demonstrate low intrasubject variability in distribution and clearance, you can use an AUC truncated at 72 hours ($AUC_{0\text{-}72}$ hr) in place of $AUC_{0\text{-}t}$ or $AUC_{0\text{-}inf}$. For drugs demonstrating high intrasubject variability in distribution and clearance, AUC truncation should not be used.

2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: EQ 80 mg Base
   Subjects: Males, general population.
   Additional Comments: See comments above

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

Bioequivalence based on (90% CI): Osimertinib

Waiver request of in vivo testing: EQ 40 mg Base based on (i) acceptable BE studies on the EQ 80 mg Base strength, (ii) comparable dissolution testing on all strengths, and (iii) proportional similarity in the formulations of 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 each of both strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In Vitro Comparative Nasogastric (NG) Tube Studies:

The approved labeling for the reference product states that the product may be administered by a nasogastric (NG) tube. Conduct the following in vitro comparative testing using 8 French NG tubes to compare the performance of the test product to that of the reference product to support NG tube administration.

NG tube preparation procedure: Prepare the NG tube studies using 12 units each of the test and the reference products by the following procedure:

a) Following the procedure described in the drug label, prepare the dispersion of one tablet at the 80 mg strength in 4 tablespoons (approximately 50 mL) of non-carbonated water at pH >7.0. Stir until the tablet is completely dispersed. Do not crush, heat, or ultrasonicate during preparation.

b) Connect an oral syringe to the NG tube, transfer the drug dispersion into the oral syringe, and pass the dispersion through the NG tube into a collection container. Rinse the original container for dispersion with 4 to 8 ounces of non-carbonated water at pH >7.0 and immediately pass the rinse through the NG tube.

c) Repeat the testing procedure described above with a fresh set of 12 units. However, after suspending the tablet content in step (a), wait 15 minutes prior to injecting the contents into the NG tube.

Comparative recovery testing: conduct comparative recovery studies to determine what percentage of the initial dose passes through a combination of oral syringe and NG tube. Follow the NG tube preparation procedure outlined above. Determine the percentage of osimertinib recovered at the tube exit relative to the initial dose for both the test and the reference products using a validated analytical method. The T/R recovery ratio and the 90% confidence interval of the T/R recovery ratio should be calculated. If high variability is observed, the applicant may increase the number of units used for this test. Visually examine the tube and the syringe for any aggregation, adherence, clogging, etc.

Risk assessment of administration conditions: NG tubes may be made with different materials (e.g., PVC, silicone, and polyurethane) which can impact the inner tube diameter. NG tubes are also available with different designs (e.g. number of ports and/or eyes; open or closed distal end) which can impact the flow of material through the tube. The applicant should consider the design of the various NG tubes that may be used for product administration, and test a representative selection (a minimum of 3) of tube designs to ensure complete delivery of the drug product. Evaluation of testing conditions may be made on the basis of recovery study (testing procedure as above) and visual analysis and documented with photographs and videos.

Standard operating procedure submission: Submit standard operating procedures for the above in vitro NG tube testing. Include details about the type of water, the pH of water, flush volume used in the studies, the tube and syringe used (e.g., material, brand, size, etc.), holding positions of the tube, shaking method of the syringe, analytical site, testing dates, etc., for each of the studies. Submit individual data, mean values, standard deviations, and coefficient of variation (% CV) in all the testing in an Excel file. Visually examine the tubing and the syringe for any aggregation, adherence, clogging, etc., and report all observations and supporting photographs. For recovery studies, video may be provided to document the testing process and associated observations. Provide explanation if additional pressure is needed to be applied during the testing to ensure complete recovery. Provide the pre-study validation report and within-study assay validation report. Conduct the above testing on unexpired test and reference batches.