Contains Nonbinding Recommendations

Draft Guidance on Atovaquone

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Atovaquone

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 250 mg
   Subjects: Normal healthy males and females, general population.
   Additional Comments: You may also consider using a parallel study design due to atovaquone's long half-life. For long half-life drug products, an AUC truncated to 72 hours may be used in place of AUC_{0-t} or $AUC_{0-\infty}$.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover *in-vivo*
   Strength: 250 mg
   Subjects: Normal healthy males and females, general population.
   Additional comments: Please see comment above.

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

Bioequivalence based on (90% CI): Atovaquone

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. 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 application.

Atovaquone is known to be practically insoluble in both water and 0.1 M HCl (<0.0002 mg/mL at 25ºC). Use of conventional aqueous dissolution media with and without surfactant has been found unsuccessful and not reproducible in some laboratories working with atovaquone tablet products. If encountering the same difficulty, you may consider developing a dissolution method

similar to the method available in the Dissolution Database. Although the use of the high alcoholic medium is not considered conventional, it has been found justifiable by the FDA for this drug substance.

You may develop an alternate dissolution testing method for the drug product and submit the dissolution testing results when the application is filed.