

**Draft Guidance on Ramelteon**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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:** Ramelteon

**Form/Route:** Tablets/Oral

**Recommended studies:** 2 Options: BCS or In-Vivo Studies

**I. BCS Waiver option:**

It may be possible to request a waiver of in-vivo testing for all the strengths of this product provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the Guidance for Industry: *Waiver of In Vivo Bioavailability and Bioequivalence for Immediate – Release Solid Oral Dosage Forms Based on the Biopharmaceutics Classification System* is submitted in the application. You may use information contained in the approved labeling of the reference product. Peer reviewed articles may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request can only be made upon review of the data submitted in the application.

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**II. In-Vivo option:**

1. Type of study: Fasting  
Design: Single-dose, two-way crossover *in vivo*  
Strength: 8 mg X 2 tablets (Dose 16 mg)  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments:

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2. Type of study: Fed  
Design: Single-dose, two-way crossover *in vivo*  
Strength: 8 mg X 2 tablets (Dose 16 mg)  
Subjects: Healthy males and nonpregnant females, general population.  
Additional Comments:

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**Analytes to measure (in appropriate biological fluid):** Ramelteon and its active metabolite monohydroxylated ramelteon (M-II) in plasma.

**Bioequivalence based on (90% CI):** Ramelteon

Please submit the metabolite data including individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and  $C_{\max}$ , as supportive evidence of bioequivalence and comparable therapeutic outcome.

**Waiver request of *in-vivo* testing:** Not Applicable

**Dissolution test method and sampling times:** Please note that **Dissolution Method 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.