Guidance on Zolpidem

This guidance represents 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: Zolpidem

Form/Route: Extended Release Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 12.5 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Patients should be advised not to drive if they are experiencing drowsiness and/or dizziness at the end of the study.

---

2. Type of study: Fed
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 12.5 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional comments: See comment above.

Analytes to measure: Zolpidem in plasma

Bioequivalence based on: Zolpidem

The 90% confidence intervals of the following PK parameters must meet the acceptable limits of [80.00-125.00]:

1. Fasting Study: Log-transformed $AUC_{0-1.5}$, $AUC_{1.5-t}$, $AUC_{0-\infty}$ and Cmax,

where $AUC_{0-1.5}$ is the area under the plasma-concentration vs. time curve from 0 to 1.5 hours, $AUC_{1.5-t}$, is area under the curve from 1.5 hours to the last measurable time point; $AUC_{0-\infty}$, is area under the curve from 0 to infinity, and Cmax, the maximum plasma concentration. The partial AUCs, $AUC_{0-1.5}$ and $AUC_{1.5-t}$, have been determined to be the most appropriate parameters for evaluation of the drug bioavailability responsible for the sleep onset and sleep maintenance phases, respectively. These two partial AUCs replace the usual AUC_{0-t}, and together with the other bioequivalence parameters, $AUC_{0-\infty}$ and Cmax, will ensure that the pharmacokinetic profiles of test and reference products are sufficiently

similar that there will be no significant difference in sleep onset, sleep maintenance, and lack of residual effects between the test and reference products.

2. Fed Study: Log-transformed AUC_{0-t}, $AUC_{infinity}$ and Cmax,

where AUC_{0-t} is the area under the curve from 0 to the last measurable time point, $AUC_{0-\infty}$, area under the curve from 0 to infinity, and Cmax, the maximum plasma concentration. These three pharmacokinetic parameters have been determined to be sufficient to establish bioequivalence under nonfasting conditions. Food delays the absorption of the reference product, and therefore, the delay due to food should eliminate the need for additional measures of early and late exposure.

Waiver request of in-vivo testing: 6.25 mg based on (i) acceptable bioequivalence studies on the 12.5 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

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.accessdata.fda.gov/scripts/cder/dissolution/. 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.

For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets. Specifications will be determined upon review of the data submitted in the application.