Contains Nonbinding Recommendations

Draft Guidance on Tretinoin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Capsule/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 10 mg
   Subjects: Healthy males. Females may be enrolled only if not of childbearing potential
   Additional Comments:
   i) Tretinoin is a known teratogen. Therefore, women of childbearing potential must be excluded from participation in the bioequivalence study. Only male subjects and postmenopausal or surgically sterilized women may be enrolled. Male subjects must use condoms when having sexual intercourse with a woman of childbearing potential, and their partners should be advised to use effective contraception until 4 weeks after the last dose is taken.
   
   ii) Applicants may consider using a reference-scaled average bioequivalence approach. If using this approach, please provide evidence of high variability in the bioequivalence parameters AUC and/or Cmax (i.e., within-subject variability > 30%). For general information on this approach, please refer to the Draft Individual Product Bioequivalence Recommendation Guidance for Progesterone Capsules currently posted on the FDA guidance website.
   
   iii) Baseline concentrations of tretinoin should be measured. Baseline concentrations should be determined for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC. Study results with and without baseline correction should be submitted.

2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: 10 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Please see comments above.

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

Recommended Sep 2010
Bioequivalence based on (90% CI): Tretinoin

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.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.