Contains Nonbinding Recommendations

Draft Guidance on Isotretinoin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Capsule/Oral

Recommended studies: 3 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover *in-vivo*
   Strength: 40 mg
   Subjects: Normal healthy males
   Additional Comments: Due to the known teratogenicity of isotretinoin, the studies should be conducted in healthy male volunteers.

   To ensure that the bioequivalence studies incorporate the appropriate safeguards against pregnancy exposure to the drug, the Agency requests that either an IND or complete protocols be submitted to the Office of Generic Drugs for review and comment prior to conducting the studies. For additional information regarding bioequivalence INDs and protocols, please refer to the CDER Manual of Policies and Procedures (MaPP) 5210.5 and 5210.6.

   The protocols for the bioequivalence studies must adhere to the components designated for all patients in the iPLEDGE program, except for obtaining registration and activation of the Prescriber (i.e., Primary Investigator), Pharmacy (i.e., person dispensing drug), and Patient (i.e., study subject). The protocol must add safety measures <u>at least as rigorous</u> as listed for all patients in the iPLEDGE program, including:

   a) Give an Accutane Medication Guide to each subject. Enroll subjects who are able to read the Accutane Medication Guide either in English or in a provided translation.

   b) Advise all subjects that isotretinoin is found in the semen of male patients taking isotretinoin, but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. While the no-effect limit for birth defects due to isotretinoin is unknown, 20 years of postmarketing reports include 4 with isolated defects compatible with the birth defects associated with isotretinoin; however 2 of these reports were incomplete, and 2 had other possible explanations for the defects observed.

c) Include all of the pertinent elements listed in the Informed Consent contained in the latest current Accutane labeling [entitled "PATIENT INFORMATION/INFORMED CONSENT (FOR ALL PATIENTS)"] in the Informed Consent to be signed by all study subjects and include requiring subject initials by key statements.

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2. Type of study: Fed
Design: Single-dose, two-way crossover *in-vivo*
Strength: 40 mg
Subjects: Normal healthy males
Additional Comments: Please see comments above.

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3. Type of study: Fasting
Design: Single-dose, two-way crossover *in-vivo*
Strength: 20 mg
Subjects: Normal healthy males
Additional Comments: Please see comments above.

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

Bioequivalence based on (90% CI): Isotretinoin

Waiver request of in-vivo testing: 10 mg and 30 mg based on (i) acceptable bioequivalence studies on the 20 mg and 40 mg strengths, (ii) proportional similarity of the formulations 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.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.