Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Isotretinoin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Isotretinoin

Dosage Form; Route: Capsule; oral

Recommended Studies: Three studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 40 mg
   Subjects: Healthy males
   Additional comments: Due to the known teratogenicity of isotretinoin, the study should be conducted in healthy males.

   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 at least as rigorous as those listed "for all patients" in the iPLEDGE program, including:

   a. Give the reference listed drug (RLD) medication guide to each subject. Enroll subjects who are able to read the RLD medication guide either in English or in a provided translation.

   b. Advise all subjects that isotretinoin is found in the semen of males 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 four with isolated defects compatible with the birth defects associated with isotretinoin; however, two of these reports were incomplete, and two had other possible explanations for the defects observed.

   c. Include all of the pertinent elements listed in the Informed Consent contained in the latest approval RLD labeling [entitled "PATIENT INFORMATION/INFORMED CONSULT (FOR ALL PATIENTS)"] in the Informed Consent to be signed by all study subjects, including requiring subject initials by key statements.

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2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 40 mg
Subjects: Healthy males
Additional comments: See comments above.

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3. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 10 mg
Subjects: Healthy males
Additional comments: See comments above.

Analyte to measure: Isotretinoin in plasma

Since isotretinoin is an endogenous substance, the plasma concentrations of isotretinoin should be corrected for baseline endogenous concentration by subtracting the mean pre-dose baseline value (average of at least three pre-dose values, e.g. -10, -2, and 0 hours). Any negative values obtained from baseline correction at time 0 hour should be designated as zero (0), and any subject with pre-dose concentration more than 5% of their Cmax should be excluded from bioequivalence statistical analysis and the 90% confidence intervals (CIs) based on the remaining subjects. The analytical method for isotretinoin measurement should have a lower limit of quantitation no greater than 1.00 ng/mL. Both baseline-corrected and uncorrected data should be submitted in the application.

Bioequivalence based on (90% CI): Baseline-corrected isotretinoin

Waiver request of in vivo testing: 20 mg, 25 mg, 30 mg, and 35 mg strengths based on (i) acceptable bioequivalence studies on the 10 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: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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 abbreviated new drug application.