Contains Nonbinding Recommendations

Guidance on Acitretin

This guidance represents 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: Acitretin

Dosage Form; Route: Capsules; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 25 mg
   Subjects: Normal healthy males, general population
   Additional comments: Due to the known teratogenicity of acitretin, bioequivalence (BE) studies should be conducted in healthy male volunteers

   To ensure that the BE studies incorporate the appropriate safeguards against pregnancy exposure to the drug, we recommend:

   a) Giving 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) Advising subjects not to donate blood during and for at least 3 years following therapy because acitretin in the blood can harm an unborn baby if the blood is given to a pregnant woman.

2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: 25 mg
   Subjects: Normal healthy males, general population
   Additional comments: Same as comments above

Analytes to measure: All-trans-acitretin and 13-*cis*-acitretin in plasma. Since acitretin undergoes extensive presystemic metabolism and interconversion by isomerization to 13-cis-acitretin, measurement of all-trans-acitretin and 13-cis-acitretin in plasma is recommended. The pharmacokinetic (PK) parameters for all-trans-acitretin should meet the current BE criteria. The 13-cis-acitretin data will be used as supportive evidence. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean PK parameters, and geometric means and ratios of means for AUC and Cmax.

Bioequivalence based on (90% CI): All-trans-acitretin

Waiver request of in vivo testing: 10 mg, 17.5 mg, and 22.5 mg strengths based on (i) acceptable BE studies on the 25 mg strength, (ii) proportional similarity 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 on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: 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 (ANDA).