Contains Nonbinding Recommendations

Draft Guidance on Ciclopirox

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Ciclopirox

Dosage Form; Route: Suspension; topical

Recommended Studies: One study

1. Type of study: Bioequivalence with Clinical Endpoint Study
   Design: Randomized, double blind, parallel, placebo-controlled in vivo
   Strength: 0.77%
   Subjects: Males and females with tinea pedis.
   Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Not Applicable.

Bioequivalence based on (90% CI): Clinical endpoint.

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.

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the guidance for industry *Controlled Correspondence Related to Generic Drug Development* and the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Additional comments regarding the bioequivalence with clinical endpoint study:

1. The Office of Generic Drugs (OGD) recommends a clinical endpoint bioequivalence study in the treatment of tinea pedis. Subjects are to be randomized to receive the generic ciclopirox topical suspension, 0.77%, the reference product, or placebo vehicle. The study drug is to be administered by gently massaging the suspension into the affected and surrounding skin areas twice daily, in the morning and evening, for 28 consecutive days (i.e., 4 weeks). The primary endpoint is to be evaluated at the test-of-cure visit (Study Week 6, 2 weeks after the end of treatment).

2. Although all tinea pedis lesions on both feet are to be treated in this study, a target lesion on one foot is to be identified as the most severe lesion and evaluated at the baseline visit and at each study visit. Each of the following signs and symptoms should be scored using the following scale:
    a. **Signs**: fissuring/cracking, erythema, maceration, and scaling
    b. **Symptoms**: pruritus and burning/stinging
    c. **Scoring Scale**: Each score should be objectively defined. The following is an example of an acceptable scale.

0	= none	(complete absence of any signs or symptoms)
1	= mild	(slight)
2	= moderate	(definitely present)
3	= severe	(marked, intense)

3. Inclusion Criteria (the sponsor may add additional criteria):
    a. Males and females aged ≥ 18 years. Sponsor may opt to also enroll pediatric subjects aged ≥ 10 years.
    b. Clinical diagnosis of tinea pedis with lesions localized to the interdigital spaces or predominantly interdigital, but may extend to other areas of the foot (the non-interdigital lesions should not be hyperkeratotic, i.e., characteristic of tinea pedis moccasin), and provisionally confirmed at baseline by a positive potassium hydroxide (KOH) wet mount preparation (i.e., skin scrapings from the target site are placed on a microscope slide with a drop of 10% KOH, and microscopic examination reveals segmented fungal hyphae).
    c. The sum of the clinical signs and symptoms scores of the target lesion is at least 4, including a minimum score of at least 2 for erythema AND a minimum score of 2 for either scaling or pruritus (on a scale of 0 to 3, where 2 indicates moderate severity).

4. Exclusion Criteria (the sponsor may add additional criteria)
    a. Pregnant or lactating or planning to become pregnant during the study period.
    b. Use of antipruritics, including antihistamines, within 72 hours prior to entry into the study.
    c. Use of topical corticosteroid, antibiotics or antifungal therapy within 2 weeks prior to entry into the study.
    d. Use of systemic (e.g., oral or injectable) corticosteroid, antibiotic or antifungal therapy within 1 month prior to entry into the study.
    e. Use of oral terbinafine or itraconazole within 2 months prior to entry into the study.

f. Use of immunosuppressive medication or radiation therapy within 3 months prior to entry into the study.
g. Confluent, diffuse moccasin-type tinea pedis of the entire plantar surface.
h. Presence of any other infection of the foot or other disease process that might confound the treatment evaluation.
i. History of dermatophyte infections unresponsive to (systemic or topical) antifungal drugs.
j. Known hypersensitivity to ciclopirox or to any of its components.

5. A positive skin fungal culture at baseline should not be an inclusion criterion due to the time lag between obtaining the culture specimen and receiving the culture results. However, a skin fungal culture must be obtained at baseline at the target site. Testing should be performed to identify the isolates at the species level (e.g., *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum*). Only subjects with a pretreatment baseline skin fungal culture from the target site that is positive for *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum* should be included in the per protocol (PP) and modified intent to treat (mITT) populations for the primary endpoint analysis. Subjects with a negative baseline fungal culture should be excluded from the PP and mITT populations but included in the safety population for the safety analyses.

6. *Trichophyton rubrum* is the most common infecting organism in tinea pedis. Therefore, > 50% of the subjects should have fungal cultures positive for *T. rubrum* upon entry into the study.

7. Subjects should avoid the use of occlusive wrappings or dressings over the application site.

8. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
    a. Any other topical products applied to the target site.
    b. Systemic (e.g., oral or injectable) antibiotics or antifungals.
    c. Systemic corticosteroid or immunosuppressive drugs.
    d. Antipruritics, including antihistamines, within 24 hours of study visits.

9. The recommended primary endpoint of the study is the proportion of subjects with therapeutic cure, defined as both mycological cure and clinical cure, at the test-of-cure visit conducted 2 weeks (+/- 4 days) after the end of treatment, (Study Day 38 to 46). Mycological cure is defined as a negative KOH test AND a negative fungal culture. Clinical cure is defined as a total severity score no more than 2 with no individual severity score greater than 1, on a 4-point scale provided above.

10. Subjects who receive or self-administer topical drug therapy to the feet for the treatment of irritation/pruritus after the treatment phase of the study should be analyzed in the mITT and PP populations as a treatment failure.

11. Subjects with a negative fungal culture at baseline should be discontinued from the study and excluded from the PP and mITT populations but included in the safety population for the safety analyses.

12. Refer to the product-specific guidance on Adapalene; Benzoyl Peroxide Topical Gel 0.3%; 2.5% for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.[1]

13. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov[2]

[1] Product-Specific Guidances for Generic Drug Development available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

[2] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm