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Draft Guidance on Butenafine Hydrochloride

October 2022

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Butenafine hydrochloride

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: (1) one in vitro bioequivalence study and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

I. Option 1: One in vitro bioequivalence study and other characterization tests

To demonstrate bioequivalence for butenafine hydrochloride topical cream, 1% using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard in the same packaging configuration that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*[a] and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

2. The test product and reference standard in the same packaging configuration should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products*

Submitted in ANDAs[a] for additional information regarding comparative Q3 characterization tests. The comparison of the test product and reference standard should include characterizations of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    - Analysis of globule size distribution
c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
    - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
    - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
d. Characterization of drying rate
e. Characterization of pH
f. Characterization of specific gravity
g. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard in the same packaging configuration should have an equivalent rate of butenafine hydrochloride release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVRT method.

    Type of study: Bioequivalence study with IVRT endpoint
    Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
    Strength: 1%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Butenafine in receptor solution
    Equivalence based on: Butenafine (IVRT endpoint: drug release rate)
    Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

II. Option 2: One in vivo bioequivalence study with clinical endpoint

1. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 1%
   Subjects: Males and non-pregnant, non-lactating females with tinea pedis
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends a bioequivalence study with clinical endpoint in the treatment of tinea pedis. Subjects are to be randomized to receive the test butenafine hydrochloride topical cream, 1%, the reference standard, or the placebo vehicle. Wash the affected skin with soap and water and dry completely before applying study drug. Apply study drug to skin between and around the toes twice daily, in the morning and evening, for 7 consecutive days (i.e., 1 week). The primary endpoint is to be evaluated at the test-of-cure visit (Study Week 6, five 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. Score each of the following signs and symptoms 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 non-pregnant, non-lactating females aged ≥ 18 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, antibiotic 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 butenafine hydrochloride or to any component of the formulations.

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, Trichophyton tonsurans,* or *Epidermophyton floccosum*). Only subjects with a pretreatment baseline skin fungal culture from the target site that is positive for *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans,* 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 5 weeks (+/- 4 days) after the end of treatment, (Study Day 38-46). 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. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoint.

12. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Additional information:

Device:
The reference listed drug (RLD) product is presented in a tube or a tube fitted with an applicator tip. The presentation in the tube with applicator tip is a drug-device combination product, and the applicator tip is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, external critical design attributes, and external operating principles of the RLD device when designing the test device.

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[b]

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.