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Draft Guidance on Luliconazole

October 2022

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Active Ingredient: Luliconazole

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 luliconazole 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 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 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 the 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 particle size distribution, crystal habit, and polymorphic form of luliconazole in the drug product
    - 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 should have an equivalent rate of luliconazole 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: Luliconazole in receptor solution
    Equivalence based on**:** Luliconazole (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 18 years of age or older, with interdigital tinea pedis due to *Trichophyton rubrum* and *Epidermophyton floccosum*
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with clinical endpoint in the treatment of interdigital tinea pedis. Subjects are to be randomized to receive the test luliconazole topical cream, 1%, the reference standard, or placebo. Sufficient study drug is to be applied to cover affected and immediate surrounding areas once daily for two weeks. The primary endpoint is to be evaluated at the test-of-cure visit (Study Week 6, four 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. The following signs and symptoms should be evaluated:
   a. Signs: fissuring/cracking, erythema, maceration, and scaling
   b. Symptoms: pruritus and burning/stinging

   Each sign and symptom 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 18 years of age or older
   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 0-3, 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, antibiotics 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, such as onychomycosis
    i. History of dermatophyte infections unresponsive to systemic or topical antifungal drugs
    j. Known hypersensitivity to luliconazole or to any component of the formulation

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*, *Epidermophyton floccosum*). Only subjects with a pretreatment baseline skin fungal culture from the target site that is positive for *Trichophyton rubrum* and *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. The reference listed drug is indicated for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum* and *Epidermophyton floccosum*. Therefore, this study is limited to subjects with fungal cultures positive for *Trichophyton rubrum* and *Epidermophyton floccosum* upon entry into the study.

7. 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

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

9. The recommended primary endpoint is the proportion of subjects with therapeutic cure at Week 6 (+/- 4 days) following 2 weeks of treatment (Study Day 38-46). Therapeutic cure defined as both mycological cure and clinical cure. Mycological cure is defined as a negative KOH test and a negative fungal culture. Clinical cure defined as total signs and symptoms severity score ≤ 2 and each sign and symptom score ≤ 1. Sign and symptoms to be assessed are erythema, maceration, scaling, fissuring/cracking, pruritus, burning/stinging on a 4-point ordinal scale; 0 = absent, 1 = mild, 2 = moderate, 3 = marked.

10. The recommended secondary endpoint of the study is the proportion of subjects with complete cure (mycological cure and clinical cure) at Week 6, where clinical cure is defined as absence of erythema, scaling, and pruritus (Grade 0 for each).

11. Provide Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Name of planned treatment
    j. Name of actual treatment
    k. Safety population flag (yes/no)
    l. Reason for exclusion from safety population
    m. mITT population flag (yes/no)
    n. Reason for exclusion from mITT
    o. PP population flag (yes/no)
    p. Reason for exclusion from PP population
    q. Randomized population flag (yes/no)
    r. Date/time of first exposure to treatment
    s. Date/time of last exposure to treatment
    t. End of study date
    u. End of study status
    v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
    w. Positive KOH wet mount preparation at baseline (yes/no)
    x. Sum of the clinical signs and symptoms scores of the target lesion at baseline
    y. Fissuring/cracking score at baseline
    z. Erythema score at baseline
    aa. Maceration score at baseline
    bb. Scaling score at baseline
    cc. Pruritus score at baseline
    dd. Burning/stinging score at baseline

ee. Final designation as therapeutic cure at Week 6 (yes/no)
ff. Complete cure at Week 6 (yes/no)
gg. Compliance rate (%)
hh. Subject missed pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
ii. Concomitant medication (yes/no)
jj. Adverse event(s) reported (yes/no)

12. Provide the Basic Data Structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Name of planned treatment
    f. Name of actual treatment
    g. Safety population flag (yes/no)
    h. mITT population flag (yes/no)
    i. PP population flag (yes/no)
    j. Analysis date
    k. Analysis visit
    l. Study visit within the designated window (yes/no)
    m. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
    n. Positive KOH wet mount preparation (yes/no)
    o. Sum of the clinical signs and symptoms scores of the target lesion
    p. Fissuring/cracking score
    q. Erythema score
    r. Maceration score
    s. Scaling score
    t. Pruritus score
    u. Burning/stinging score
    v. Additional treatment required during the visit (yes/no)
    w. Adverse event reported during the visit (yes/no)
    x. Concomitant medication during the visit (yes/no)

13. 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 BE studies with clinical endpoint.

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

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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.