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Draft Guidance on Ketoconazole

October 2022

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Active Ingredient: Ketoconazole

Dosage Form; Route: Gel; 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 ketoconazole topical gel, 2% 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 product 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
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.
d. Characterization of specific gravity
e. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of ketoconazole 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: 2%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Ketoconazole in receptor solution
    Equivalence based on**:** Ketoconazole (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 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: 2%
    Subjects: Males and non-pregnant, non-lactating females with seborrheic dermatitis
    Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a single bioequivalence study with clinical endpoint in the treatment of seborrheic dermatitis comparing the topical gel, 2% test product versus the reference standard and placebo (vehicle) control, each applied once daily to the affected area(s) for 14 days (2 weeks). The primary endpoint, overall cure, is to be evaluated at the end of the follow-up period (Study Day 28; Week 4).

2. Inclusion Criteria:
    a. Males or non-pregnant non-lactating females aged ≥ 12 years with a clinical diagnosis of seborrheic dermatitis. Affected area(s) in at least one of the following locations: scalp, face [e.g., hairline, eyebrow(s), bridge of nose, naso-labial fold(s)], behind the ears, chest and upper back.
    b. Baseline erythema score of at least 2, baseline scaling score of at least 2 and baseline pruritus score of at least 1 (per Scale 1).
    c. Baseline Investigator's Global Assessment (IGA) seborrheic dermatitis score of at least 3 (per Scale 2).
    d. Willing to refrain from use of all other topical medications or antibiotics during the treatment and observation periods (i.e., from Day 0 through Day 28).
    e. If female of childbearing potential, the subject had a negative result for a pregnancy test having sufficient sensitivity for hCG within 2 weeks prior to starting treatment and is willing to use an acceptable form of birth control throughout the study.

3. Exclusion Criteria:
    a. Clinically significant systemic disease (e.g., immunological deficiencies, AIDS, current malignancies, uncontrolled diabetes mellitus).
    b. Presence of any skin condition that would interfere with the diagnosis or assessment of seborrheic dermatitis (e.g., atopic dermatitis, psoriasis, acne).
    c. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of seborrheic dermatitis.
    d. History of hypersensitivity or allergy to ketoconazole and/or any component of the test or reference product.
    e. Use within 6 months prior to baseline of oral retinoids (e.g., Accutane) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
    f. Use within 1 month prior to baseline of 1) systemic antifungals, 2) systemic steroids, 3) systemic antibiotics, 4) systemic anti-inflammatory agents or 5) cytostatic or immunomodulating drugs (e.g., cyclosporine, tacrolimus, pimecrolimus).
    g. Use within 2 weeks prior to baseline of 1) topical steroids, 2) topical retinoids, 3) topical antifungal treatments including over-the-counter preparations, 4) topical anti-inflammatory agents, 5) topical antibiotics or 6) topical treatment for seborrheic dermatitis (e.g., coal tar preparations, antiseborrheic and antidandruff shampoos).

4. Scales to be used for evaluation of baseline disease severity and treatment effect:

Scale 1. Sample Sign and Symptom Scales for Erythema, Scaling and Pruritus

Symptom	Score	Description
Erythema	0	**None**: No evidence of erythema
	1	**Mild**: Barely perceptible erythema which is faint or patchy, blanches easily to the touch
	2	**Moderate**: Distinct erythema, more difficult to blanch
	3	**Severe**: Intense (fiery red) erythema, does not blanch
Scaling	0	**None**: No scaling evident on lesions
	1	**Mild**: Barely detectable, scattered, small flaking scales
	2	**Moderate**: Scales clearly visible and prominent
	3	**Severe**: Coarse, thick scales, with flaking into clothes or skin
Pruritus	0	**None**: No evidence of pruritus
	1	**Mild**: Present with minimal discomfort
	2	**Moderate**: Appreciable discomfort which interferes with daily activities
	3	**Severe**: Extreme discomfort which prevents the completion of daily activities and may disrupt sleep

Scale 2. Sample IGA Scale for Seborrheic Dermatitis Overall Status of Disease Severity

Score	Description
0	**Complete clear**
1	**Almost Clear**: Only slight pink color or trace amounts of scaling
2	**Mild**: Pink to red color, or slight scaling
3	**Moderate**: Distinct redness or clearly visible scaling
4	**Severe**: Severe score in erythema or scaling

5. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
    a. Any over the counter (OTC) or prescription topical or systemic treatment for seborrheic dermatitis, including medicated shampoos to treat seborrheic dermatitis of the scalp.
    b. Topical product other than the assigned treatment (including moisturizers, new brands of make-up, creams, ointments, lotions, and powders) applied on or near the treatment area.
    c. More than 10,000 IU/day of Vitamin A supplements.
    d. Spironolactone.
    e. Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed) or other systemic treatment for acne vulgaris.

f. Systemic (e.g., oral or injectable) antifungals.
g. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
h. Radiation therapy.
i. Antipruritics, including antihistamines, within 24 hours of study visits.
j. Subjects should be instructed to avoid using study product near fire, flame or smoking during and immediately following application, to not allow the gel to come in contact with the eyes, nostrils, or mouth, and to always wash hands thoroughly after application of study medication.

6. The recommended primary endpoint is overall cure at Day 28 (Week 4; 2 weeks after end of treatment) of the study. Overall cure is defined as erythema and scaling scores of 0 (none) if the baseline score was 2 or ≤ 1 (mild) if the baseline score was 3 AND Investigator Global Assessment score of ≤ 1 (completely clear or almost clear).

7. Application site reactions such as dryness, burning/stinging, erosion, edema and pain are to be recorded at each visit to allow a comparison between treatment groups. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.

8. Provide the 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
    d. Site identifier: study center
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Name of planned treatment
    j. Name of actual treatment
    k. Location of treatment area(s)
    l. Duration of treatment (total exposure in days)
    m. Completed the study (yes/no)
    n. Reason for premature discontinuation of subject
    o. Subject required additional treatment for seborrheic dermatitis due to unsatisfactory treatment response (yes/no)
    p. Per Protocol (PP) population inclusion (yes/no)
    q. Reason for exclusion from PP population
    r. Modified Intent to Treat (mITT) population inclusion (yes/no)
    s. Reason for exclusion from mITT population
    t. Safety population inclusion (yes/no)
    u. Reason for exclusion from Safety population
    v. Erythema score at baseline

w. Scaling score at baseline
x. Pruritus score at baseline
y. IGA score at baseline
z. Erythema score at Day 28 (Week 4)
aa. Scaling score at Day 28 (Week 4)
bb. Pruritus score at Day 28 (Week 4) aa. IGA score at Day 28 (Week 4
cc. Final designation: (success/failure)
dd. Treatment compliance: number of missed doses per subject
ee. Concomitant medication (yes/no)
ff. Adverse event(s) reported (yes/no)

9. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headers, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier
    d. Name of planned treatment
    e. Name of actual treatment
    f. Location(s) of dose administration: application site(s)
    g. Visit number
    h. Visit date
    i. Number of days since baseline visit
    j. Evaluator: identity of evaluator
    k. Erythema score
    l. Scaling score
    m. Pruritus score
    n. IGA score
    o. Skin reaction scores for each sign and symptom evaluated (e.g., dryness, burning/stinging, erosion, edema, pain, etc.)
    p. Concomitant medication reported during this visit (yes/no)
    q. Adverse event reported during this visit (yes/no)
    r. Laboratory testing during this visit (yes/no)

10. 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.

11. 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.