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Draft Guidance on Tazarotene

October 2022

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Active Ingredient: Tazarotene

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 tazarotene topical gel, 0.05% 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 tazarotene in the drug product
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 pH
e. Characterization of specific gravity
f. Characterization of any other potentially relevant Q3 attributes.

3. The test product and reference standard should have an equivalent rate of tazarotene 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: 0.05%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Tazarotene in receptor solution
    Equivalence based on**:** Tazarotene (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: 0.05%
   Subjects: Males and non-pregnant, non-lactating females with clinical diagnosis of plaque psoriasis
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a bioequivalence study with a clinical endpoint in the treatment of stable plaque psoriasis comparing the test product versus the reference standard and vehicle control, each administered once daily, in the evening, to psoriatic lesions for 84 days (12 weeks). The primary endpoint is the proportion of subjects with treatment success at the end of treatment (Study Day 84).

2. Enough gel should be applied (2 mg/cm^2) to cover only the lesions with a thin film. If a bath or shower it taken prior to application, the skin should be dry before applying the gel. If emollients are used, they should be applied at least an hour before applying the gel.

3. Inclusion Criteria (the sponsor may add additional criteria):
   a. Males or non-pregnant, non-lactating females ≥ 18 years of age with a clinical diagnosis of stable (at least 6 months) plaque psoriasis involving at least 2% and no more than 20% body surface area (BSA), not including the scalp and intertriginous areas.
   b. An Investigator's Global Assessment (IGA) of disease severity of at least moderate severity (score ≥ 3, per Table 1) as an overall assessment of all lesions to be treated.
   c. A minimum plaque elevation of at least moderate severity (grade ≥ 3, per Table 2) at the target lesion site. The most severe lesion at baseline should be identified as the target lesion.
   d. If female of childbearing potential, the subject must have a negative result for a pregnancy test having sensitivity down to at least 50 mIU/mL for hCG within 2 weeks prior to starting treatment, begin treatment during a normal menstrual period, and be willing to use an acceptable form of birth control throughout the study.

4. Exclusion Criteria (the sponsor may add additional criteria):
   a. Females who are pregnant, breast feeding, planning a pregnancy or do not agree to use an acceptable form of birth control throughout the study
   b. Females of childbearing potential who do not agree to utilize an adequate form of contraception
   c. Current diagnosis of unstable forms of psoriasis in the treatment area, including guttate, erythrodermic, exfoliative or pustular psoriasis

d. Other inflammatory skin disease in the treatment area that may confound the evaluation of the plaque psoriasis (e.g., atopic dermatitis, contact dermatitis, eczema, tinea corporis)
e. Presence of pigmentation, extensive scarring, pigmented lesions, or sunburn in the treatment areas, which could interfere with the rating of efficacy parameters
f. History of psoriasis unresponsive to topical treatments
g. History of hypersensitivity or allergy to tazarotene, retinoids and/or any component of the test or reference product
h. Current immunosuppression
i. Use within six months prior to baseline of biologic treatment for psoriasis (e.g., infliximab, adalimumab, alefacept)
j. Use within three months prior to baseline of: 1) chemotherapy, or 2) radiation therapy
k. Use within two months prior to baseline of any immunosuppressive drugs (e.g., tacrolimus, pimecrolimus) or oral retinoids
l. Use within one month prior to baseline of: 1) systemic steroids, 2) systemic antibiotics, 3) systemic antipsoriatic treatment (e.g., methotrexate, cyclosporine, hydroxyurea), 4) psoralen and ultraviolet A (PUVA) therapy, 5) ultraviolet B (UVB) therapy or 6) systemic anti-inflammatory agents
m. Use within 2 weeks prior to baseline of: 1) topical anti-psoriatic drugs (e.g., salicylic acid, anthralin, coal tar, calcipotriene, tazarotene), 2) topical corticosteroids or 3) topical retinoids

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

Table 1. IGA of Disease Severity

Score	Grade	Definition
0	None	No plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale; no erythema
1	Minimal	Essentially flat with possible trace elevation; faint erythema; no psoriatic scale
2	Mild	Slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered
3	Moderate	Moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarse scales with most lesions partially covered
4	Severe	Marked elevation with hard, sharp edges to plaque; severe erythema (very red coloration); coarse, thick scales with virtually all lesions covered and a rough surface
5	Very Severe	Very marked elevation with very hard, sharp edges to plaque; very severe erythema (extreme red coloration); very coarse, thick scales with all lesions covered and a very rough surface

Table 2. Psoriasis Area Severity Index (PASI) at the Target Lesion Site

Score	Grade	Erythema	Scaling	Plaque Elevation
0	Clear	No evidence of erythema	No evidence of scaling	No evidence of plaques above normal skin level
1	Almost Clear	Pink discoloration, minimal erythema	Occasional fine scales hardly noticeable	Slight, just discernable elevation above normal skin level
2	Mild	Light red coloration	Slight but definite roughness, fine scale present, no cracking	Discernable elevation above normal skin level upon examination, but not pronounced
3	Moderate	Moderate redness, but not dark	Moderate roughness, somewhat coarse scaling	Definite plaque formation with rounded/sloped edges to plaque
4	Severe	Dark red coloration	Marked roughness, coarse/thick scaling, cracking may be evident	Marked elevation with hard, distinct edges to plaque
5	Very Severe	Very dark red coloration with induration present	Very thick scales covering extensive area severe cracking/fissures may be evident	Very marked elevation, very hard and sharp edges to plaque

6. BSA percentage is no longer requested as an individual component sign in the PASI scale but the information of BSA percentage and distribution should be collected at baseline.

7. Tazarotene gel is contraindicated during pregnancy. Therefore, in a bioequivalence study with clinical endpoint, all females of childbearing potential should be maintained on an appropriate method of contraception throughout the study. The informed consent form must clearly discuss the potential risk of teratogenicity.

8. It is recommended to repeat the urine pregnancy test (with sensitivity down to at least 50 mIU/mL hCG) for all females of childbearing potential during the study visits at Study Day 28 (Week 4), Study Day 56 (Week 8) and end-of-treatment (Study Day 84; Week 12). If a female of childbearing potential discontinues prematurely, the pregnancy test should be performed at the exit visit.

9. 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. 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.
    b. Topical or systemic antipsoriatic treatment (e.g., anthralin, coal tar, tazarotene, retinoids, tacalcitol, infliximab, adalimumab, alefacept, PUVA therapy, UVB therapy).
    c. Topical or systemic corticosteroids.

d. Photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides).
e. Immunosuppressive drugs.
f. More than 10,000 IU/day of Vitamin A supplements.
g. Initiation of or changes to non antipsoriatic concomitant medication that could affect psoriasis (e.g., beta blockers, lithium) during the study.
h. Tanning booths, sun lamps, or non-prescription ultraviolet light sources.
i. Phototherapy.
j. Application of study treatment to unaffected skin.
k. The treated areas should not be bandaged, covered or wrapped as to be occlusive.
l. Subjects should be instructed to minimize exposure to natural sunlight, to use sunscreens of at least SPF 15 and wear protective clothing during the day, to not allow the gel to come in contact with the eyes, eyelids, or mouth, to not use study treatment on skin that has eczema, and to always wash hands thoroughly after application of study medication.

10. The recommended primary endpoint is the proportion of subjects with treatment success (defined as "absent, very mild, or mild disease, a score of 0, 1 or 2, within the treatment area") on the IGA at the Week 12 visit (Study Day 84).

11. The site and size of the treatment area should be tabulated and compared between treatment groups.

12. 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.

13. 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.