

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Tazarotene

August 2021

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This guidance, which interprets the Agency’s regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

In February 2019, FDA issued a draft product-specific guidance for industry on generic tazarotene. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Tazarotene

Dosage Form; Route: Cream; topical

Recommended Study: One study

1. Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double blind, parallel, placebo controlled, in vivo
Strength: 0.05%
Subjects: Males and nonpregnant, nonlactating females with clinical diagnosis of plaque psoriasis
Additional comments: Specific recommendations are provided below.

Analyte to measure: Not applicable

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

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 study with clinical endpoint:

1. The Office of Generic Drugs recommends conducting a bioequivalence study with a clinical endpoint in the treatment of stable plaque psoriasis comparing the test product versus the reference product 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 cream should be applied (2 mg/cm²) to cover only the lesions with a thin film. If a bath or shower is taken prior to application, the skin should be dry before applying the cream.
3. Inclusion Criteria (the sponsor may add additional criteria)
 - a. Male or nonpregnant, nonlactating 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 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 nonerythematous 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
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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 cream 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 nonprescription 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 cream 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. Please refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled *Guidance on Adapalene; Benzoyl Peroxide* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.
13. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov¹.

Revision History: Recommended April 2011; Revised February 2019, August 2021

Unique Agency Identifier: PSG_021184-Cre-0.05P

¹ Study Data Standards Resources: <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>