

Draft Guidance on Calcipotriene

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Calcipotriene

Dosage Form; Route: Ointment; topical

Recommended Studies: One study

Type of study: Bioequivalence Study with Clinical Endpoint

Design: Randomized, double blind, parallel, placebo controlled, in vivo

Strength: 0.005%

Subjects: Males and nonpregnant females with clinical diagnosis of plaque psoriasis

Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): 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 (OGD) 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 placebo control, each administered once daily to the affected area for 56 days (8 weeks). The two co-primary endpoints are the proportions of subjects with treatment success on the Physician's Global Assessment (PGA) and clinical success on the Psoriasis Area Severity Index (PASI) scale at the end of treatment (study Day 56).

2. Inclusion Criteria (the sponsor may add additional criteria)
 - a. Male or nonpregnant females with a clinical diagnosis of stable (at least 3 months) plaque-type psoriasis involving 5 to 20% BSA, not including the face, scalp, groin, hands, and feet.
 - b. A PGA of disease severity of at least moderate disease severity (grade ≥ 3 , per Table 1).
 - 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.

Table 1. Physician’s Global Assessment (PGA) of Disease Severity

Score	Grade	Definition
0	None	No plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale
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. Severity of 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	Marked roughness,	Marked elevation with

		coloration	coarse/thick scaling, cracking may be evident.	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

4. Body Surface Area (BSA) percentage is no longer requested as an individual component sign in the PASI scale but the BSA percentage and distribution should be recorded at Baseline.
5. Exclusion Criteria (the sponsor may add additional criteria)
 - a. Females who are pregnant, breast feeding, or planning a pregnancy.
 - b. Current diagnosis of unstable forms of psoriasis in the treatment area, including guttate, erythrodermic, exfoliative or pustular psoriasis.
 - c. Other inflammatory skin disease in the treatment area that may confound the evaluation of the plaque psoriasis (e.g., atopic dermatitis, contact dermatitis, tinea corporis).
 - d. Presence of pigmentation, extensive scarring, or pigmented lesions in the treatment areas, which could interfere with the rating of efficacy parameters.
 - e. History of psoriasis unresponsive to topical treatments.
 - f. History of hypersensitivity to any component of the test or reference product.
 - g. Current or past history of hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders.
 - h. Current immunosuppression.
 - i. Use within one month prior to baseline of: 1) systemic steroids, 2) systemic antibiotics, 3) systemic antipsoriatic treatment, 4) PUVA therapy, 5) UVB therapy, or 6) systemic anti-inflammatory agents.
 - j. 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, 3) immunosuppressive drugs (e.g., tacrolimus, pimecrolimus), or 4) topical retinoids.
6. 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. Immunosuppressive drugs.
 - e. Calcium supplements.
 - f. More than 400 IU/day of Vitamin D or vitamin D analogs.

- 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 UV light sources.
 - i. Phototherapy.
 - j. The treated areas should not be bandaged, covered or wrapped as to be occlusive.
 - k. Subjects should be instructed to minimize exposure to natural sunlight, to not allow the ointment to come in contact with the face or eyes and to always wash hands thoroughly after use.
7. The recommended co-primary endpoints are:
- a. the proportion of subjects in each treatment group with treatment success (defined as absent or very mild disease, a score of 0 or 1, within the treatment area) on the PGA of disease severity at the Week 8 visit (Study Day 56), and
 - b. the proportion of subjects in each treatment group with clinical success (defined as absent or mild, a score of 0 or 1, at the target lesion site) on the PASI at the week 8 visit (Study Day 56). Each psoriatic sign of scaling, erythema, and plaque elevation should have a score of 0 or 1 at Week 8 (Study Day 56) for the subject to be considered a success. The target lesion is to be identified at Baseline as the most severe lesion.
8. Due to the possibility of elevated serum calcium levels with calcipotriene absorption, serum calcium, serum albumin and albumin-corrected serum calcium levels should be included in serum chemistry analysis. Subjects with elevation in serum calcium outside the normal range should be discontinued from the study. The serum calcium level should be corrected for serum albumin level as follows:
- $$\text{“corrected” serum calcium} = \text{serum calcium mg/dL} + (0.8 \times [4.0 - \text{albumin g/dL}])$$
9. Calcium levels of subjects in study treatment groups should be evaluated to ensure similar effects are seen with both active treatments. The number of subjects with elevated serum calcium levels and the mean albumin corrected calcium levels at Baseline and at Week 8 should also be compared in all study treatment groups.
10. The site and size of the treatment area should be compared and tabulated for each treatment group.
11. Refer to the product-specific guidance on Adapalene; Benzoyl Peroxide Topical Gel 0.3%; 2.5% for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.¹
12. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov²

¹ Product-Specific Guidances for Generic Drug Development available at:
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>

² Study Data Standards for Submission to CDER and CBER available at:
<https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm>