

Draft Guidance on Betamethasone Dipropionate; Calcipotriene

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Active Ingredient: Betamethasone dipropionate; Calcipotriene

Dosage Form; Route: Suspension; topical

Recommended Studies: Two options: (1) one in vitro bioequivalence study and other characterization tests or (2) one in vivo (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint and one in vivo bioequivalence study with clinical endpoint

I. Option 1: One in vitro bioequivalence study and other characterization tests

To demonstrate bioequivalence for betamethasone dipropionate and calcipotriene topical suspension, 0.064%; 0.005% 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 with respect to the reference standard 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 the drug substance(s) 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 specific gravity
 - e. Characterization of any other potentially relevant Q3 attributes
3. The test product and reference standard should have an equivalent rate of betamethasone dipropionate and calcipotriene 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: 0.064%; 0.005%

Test system: A synthetic membrane in a diffusion cell system

Analytes to measure: Betamethasone dipropionate and calcipotriene in receptor solution

Equivalence based on: Betamethasone dipropionate and calcipotriene (IVRT endpoint: drug release rate)

Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test (IVRT) 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 (vasoconstrictor) bioequivalence study with pharmacodynamic endpoint and one in vivo bioequivalence study with clinical endpoint

1. A. Type of study: Pilot vasoconstrictor study
Design: A pilot dose duration-response study using the reference standard
Strength: 0.064%; 0.005%
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: Refer to the most recent version of the FDA guidance for industry on *Topical Dermatological Corticosteroids: In Vivo Bioequivalence*.^a
- B. Type of study: Pivotal vasoconstrictor bioequivalence study
Design: A pivotal bioequivalence study
Strength: 0.064%; 0.005%
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above.
2. Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double blind, parallel, placebo-controlled, in vivo
Strength: 0.064%; 0.005%
Subjects: Males and non-pregnant, non-lactating females with clinical diagnosis of scalp 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 scalp psoriasis comparing the test product versus the reference standard and vehicle control, each applied once daily to the affected area(s) of the scalp for 4 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 target lesion site at the end of treatment (Study Week 4).
2. Inclusion Criteria (the sponsor may add additional criteria):
 - a. Males or non-pregnant females aged at least 18 years with a clinical diagnosis of stable (at least 6 months) scalp psoriasis involving at least 10% of the scalp and clinical signs of psoriasis vulgaris on trunk and/or limbs.
 - b. A PGA of disease severity of the scalp psoriasis consistent with at least moderate disease severity (grade ≥ 3 , per Table 1).
 - c. A plaque elevation of at least moderate severity (grade ≥ 3 , per Table 2) at the scalp target lesion site. The most severe scalp 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; 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. 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	Moderate	Definite plaque

		redness, but not dark	roughness, somewhat coarse scaling	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

3. Exclusion Criteria (the sponsor may add additional criteria):

- a. Females who are pregnant, breast feeding, or planning a pregnancy.
- b. Females of childbearing potential who do not agree to utilize an adequate form of contraception.
- c. Current diagnosis of unstable forms of psoriasis including guttate, erythrodermic, exfoliative or pustular psoriasis.
- d. Other inflammatory skin disease in the scalp that may confound the evaluation of the scalp psoriasis (e.g., atopic dermatitis, contact dermatitis, tinea capitis).
- e. Presence of pigmentation, extensive scarring, pigmented lesions or sunburn in the scalp, which could interfere with the rating of efficacy parameters.
- f. History of psoriasis unresponsive to topical treatments.
- g. History of hypersensitivity to any component of the test product or reference standard.
- h. Current or past history of hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders.
- i. Current immunosuppression.
- j. Use within six months prior to baseline of biologic treatment for psoriasis (e.g., infliximab, adalimumab, alefacept).
- k. Use within three months prior to baseline of: 1) chemotherapy, or 2) radiation therapy.
- l. Use within two months prior to baseline of: 1) immunosuppressive drugs (e.g., tacrolimus, pimecrolimus), or 2) oral retinoids.
- m. Use within one month prior to baseline of: 1) systemic steroids, 2) systemic antibiotics, 3) other systemic antipsoriatic treatment, 4) PUVA therapy, 5) UVB therapy, or 6) systemic anti-inflammatory agents.

- n. 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.
4. Body Surface Area (BSA) percentage and distribution, as well as the scalp surface area affected with psoriasis, should be recorded at baseline.
5. 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:
“corrected” serum calcium=serum calcium mg/dL + (0.8 x[4.0-albumin g/dL])
6. 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 4 should also be compared in all study treatment groups.
7. The recommended co-primary endpoints are both:
 - 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(s)) on the PGA of disease severity at the Week 4 visit.
 - 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 4 visit. Each psoriatic sign of scaling, erythema, and plaque elevation should have a score of 0 or 1 at week 4 for the subject to be considered a success. The target lesion is to be identified at baseline as the most severe lesion.
8. The site and size of the treatment area should be compared and tabulated for each treatment group.
9. 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.
10. 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>.