Contains Nonbinding Recommendations

Draft Guidance on Betamethasone Dipropionate; Calcipotriene Hydrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Betamethasone dipropionate; Calcipotriene hydrate

Dosage Form; Route: Ointment; topical

Recommended studies: Three studies

1.&2. Type of study: Vasoconstrictor Study
Design: Evaluate the betamethasone dipropionate component by conducting a pilot dose duration-response study followed by the pivotal in vivo bioequivalence study.
Strength: 0.064%; 0.005%
Subjects: Males and females, general population
Additional comments: Please refer to the guidance "Topical Dermatological Corticosteroids: In Vivo Bioequivalence" available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070234.pdf.

---

3. 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 females with clinical diagnosis of psoriasis vulgaris (plaque psoriasis)
Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Not Applicable

Bioequivalence based on (90% CI): Vasoconstrictor assay studies (pilot dose duration-response study followed by the pivotal in vivo bioequivalence study); Clinical endpoint (study #3)

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 psoriasis vulgaris comparing the test product versus the reference product and vehicle control, each applied once daily as an adequate layer to the affected area(s) for 28 days (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 Week 4 visit (Study Day 29).

2. Inclusion Criteria (the sponsor may add additional criteria)
   a. Male or nonpregnant females aged at least 18 years with a clinical diagnosis of stable (at least 6 months) psoriasis vulgaris involving 5% to 30% body surface area (BSA).
   b. A PGA of disease severity of 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 target lesion site. The most severe lesion at Baseline should be identified as the target lesion.

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 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 psoriasis vulgaris (e.g., atopic dermatitis, contact dermatitis, 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 to any component of the test or reference product.
   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. Scales to be used for evaluation of baseline disease severity and treatment effect:

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 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

5. 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.

6. 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])

7. Calcium levels of subjects should be compared between study treatment groups to ensure that 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.

8. 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(s)] on the PGA of disease severity at the Week 4 visit (Study Day 29), 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 4 visit (study day 29). Each psoriatic sign of scaling, erythema, and plaque elevation should have a score of 0 or 1 at Week 4 (Study Day 29) for the subject to be considered a success. The target lesion is to be identified at Baseline as the most severe lesion.

9. The site and size of the treatment area should be compared and tabulated for each treatment group.

10. 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]

11. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov[2]

[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