Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Tapinarof

November 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Tapinarof

Dosage Form: Cream

Route: Topical

Strength: 1%

Recommended Study: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double-blind, parallel-group, placebo-controlled, in vivo
   Strength: 1%
   Subjects: Male and non-pregnant, non-lactating female adults (age ≥18 years) with a clinical diagnosis of plaque psoriasis
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the one comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of stable plaque psoriasis comparing the test product versus the reference standard and vehicle control, each applied to the affected areas once daily. The primary endpoint is the proportion of subjects with treatment success (defined as a Physician Global Assessment (PGA) score of clear (0) or almost clear (1) with a minimum 2-grade improvement from baseline at the end of treatment (Week 12; Study Day 84)).

2. Inclusion criteria (the sponsor may add additional criteria):
    a. Male or non-pregnant, non-lactating females with a clinical diagnosis of stable (at least 6 months) plaque psoriasis involving 3 to 20% body surface area (BSA), not including the face, scalp, groin, palms, and soles in the BSA calculation
    b. A PGA score of 2 (mild), 3 (moderate), or 4 (severe) as shown in Table 1

Table 1. PGA of Disease Severity

Score	Category	Definition
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable erythema; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

3. Exclusion criteria (the sponsor may add additional criteria):
    a. Females who are pregnant, breast feeding, or who wish to become pregnant during the study period
    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 hypersensitivity to any component of the test product or reference standard
    f. Current immunosuppression
    g. Use within one month or within 5 half-lives (whichever is longer) prior to baseline of: (1) systemic steroids, (2) systemic antibiotics, (3) systemic antipsoriatic treatment, (4) psoralen plus ultraviolet A (PUVA) therapy, (5) ultraviolet B (UVB) therapy, or (6) systemic anti-inflammatory agents
    h. 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

4. 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. Initiation of or changes to non-antipsoriatic concomitant medication that could affect psoriasis (e.g., beta blockers, lithium) during the study
f. Tanning booths, sun lamps, or nonprescription UV light sources
g. Phototherapy
h. The treated areas should not be bandaged, covered or wrapped as to be occlusive
i. 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

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

6. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[a] for a recommended approach to statistical analysis and study design for the comparative clinical endpoint bioequivalence study.

7. Refer to the Study Data Standards Resources website https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*[b] and the most recent version of the FDA guidance for industry *on Formal Meetings between FDA and ANDA Applicants of Complex Products Under GDUFA*[b] for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Document History: Recommended November 2023

Unique Agency Identifier: PSG_215272

[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.