

Draft Guidance on Imiquimod

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Cream; topical

Recommended Studies: One study

1. Type of study: Bioequivalence with Clinical Endpoint Study
Design: Randomized, double blind, parallel, placebo-controlled, in vivo.
Strength: 3.75%
Subjects: Immunocompetent males and nonpregnant, nonlactating females with clinically typical, visible or palpable actinic keratoses (AK) on the face or balding scalp.
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 with clinical endpoint study:

1. The Office of Generic Drugs (OGD) recommends a clinical endpoint bioequivalence study in the treatment of actinic keratoses (AK). Subjects are to be randomized to receive the generic imiquimod topical cream, 3.75%, the reference product, or placebo vehicle. A placebo control arm is especially important when studying a disease such as AK, in which spontaneous resolution may occur. The study drug is to be applied once daily for two 2-week treatment cycles separated by a 2-week no-treatment period to the entire designated treatment area (either the entire face or balding scalp) just before normal sleeping hours, left on the skin for approximately 8 hours, and then removed by washing

the area with mild soap and water. Hand washing before and after cream application is recommended. The primary endpoint is to be evaluated at Study Week 14 (8 weeks after completion of treatment).

2. Inclusion Criteria (the sponsor may add additional criteria):
Immunocompetent male or nonpregnant, nonlactating female at least 18 years of age with at least five (5) and no more than twenty (20) clinically typical, visible or palpable AK lesions, each at least 4 mm in diameter, in an area that exceeds 25-cm² on either the face (excluding ear) or balding scalp, but not both.
3. Exclusion Criteria (the sponsor may add additional criteria):
 - a. Presence of atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, or other possible confounding skin conditions on face or balding scalp.
 - b. Use within 6 months prior to randomization on the face or balding scalp of 1) chemical peel, 2) dermabrasion, 3) laser abrasion, 4) PUVA (psoralen plus ultraviolet A) therapy, or 5) UVB therapy.
 - c. Use within 1 month prior to randomization on the face or scalp of 1) cryodestruction or chemodestruction, 2) curettage, 3) photodynamic therapy, 4) surgical excision, 5) topical 5-fluorouracil, 6) topical corticosteroids 7) topical diclofenac, 8) topical imiquimod, 9) topical retinoids, or 10) other treatments for AK.
 - d. Use within 1 month prior to randomization of 1) immunomodulators or immunosuppressive therapies, 2) interferon, 3) oral corticosteroids or 4) cytotoxic drugs.
 - e. Known allergies to imiquimod or any excipients in the test or reference product.
4. Subjects should not apply moisturizers, sun screen, make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Subjects should not use any type of bandage or occlusive dressing on the treatment area or apply the cream to open skin wounds, infections or exfoliative dermatitis. Subjects should avoid exposure to sunlight, the use of tanning booths, sunlamps, or nonprescription UV light sources, or contact of the study drug with the eyes, lips, or nostrils.
5. The protocol should include a list of the prescription and over-the-counter drug products and treatments that are prohibited during the study, such as:
 - a. Any therapy for AK, such as prescription topical retinoids, topical diclofenac, topical salicylic acid, bichloroacetic acid, trichloroacetic acid, cryodestruction, chemodestruction, surgical excision, CO₂ laser vaporization, electrocautery, photodynamic therapy, or curettage.
 - b. Immunomodulators or immunosuppressive therapies, interferon, oral corticosteroids, cytotoxic drugs, systemic corticosteroids, or topical steroids anywhere on the head.
6. The recommended primary endpoint of the study is the proportion of subjects in the per protocol (PP) population with treatment success (100% clearance of all AK lesions within the treatment area) at Study Week 14 (8 weeks after completion of treatment). All AK

(i.e., baseline AK and any new AK) within the treatment area are to be treated and included in the efficacy lesion count for each visit.

7. 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
8. 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>