

Contains Nonbinding Recommendations
Draft Guidance on Ingenol Mebutate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Gel; topical

Recommended Studies: One study

1. Type of study: Bioequivalence with Clinical Endpoint Study
Design: Randomized, double blind, parallel, placebo-controlled, in vivo.
Strength: 0.05%
Subjects: Immunocompetent males and nonpregnant, nonlactating females with clinically typical, visible or palpable actinic keratoses (AK) on the trunk or extremities.
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 bioequivalence study with clinical endpoint in the treatment of actinic keratoses (AK). Subjects are to be randomized to receive the generic ingenol mebutate gel 0.05%, the reference product, or placebo vehicle. The study drug is to be applied once daily for 2 days to the selected treatment area on the trunk or extremities, up to one contiguous skin area of approximately 25 cm² (e.g., 5 cm x 5 cm) using one unit dose tube, left on the skin for a period of 6 hours, and then removed by washing the area with mild soap and water. Subjects should take care not to transfer the applied drug to other areas, including the eye. Hand washing

immediately after application is recommended. The primary endpoint is to be evaluated at Day 57.

2. Inclusion Criteria (the sponsor may add additional criteria):
 - Immunocompetent male or nonpregnant, nonlactating female at least 18 years of age with four (4) to eight (8) clinically typical AK lesions, each at least 4 mm in diameter, within a contiguous 25 cm² treatment area located on the trunk or extremities.
3. Exclusion Criteria (the sponsor may add additional criteria):
 - a. Presence of atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, xeroderma pigmentosum or other possible confounding skin conditions on trunk or extremities.
 - b. Location of selected treatment area is (1) within 5 cm of an incompletely healed wound or (2) in an area or lesion that was previously treated with ingenol mebutate.
 - c. Use within 2 weeks of baseline visit on trunk or extremities (1) cryodestruction or chemodestruction (2) surgical excision, (3) curettage, (4) dermabrasion (5) chemical peel, (6) laser resurfacing (7) acid-containing therapeutic products, (8) topical retinoids (9) medicated or irritant topical salves, (10) artificial tanners, (11) topical steroids.
 - d. Use within 4 weeks of baseline visit on trunk or extremities, (1) immunomodulators, (2) cytotoxic drugs, (3) interferon/interferon inducers, (4) systemic medications that suppress the immune system, (5) psoralen plus ultraviolet A (PUVA) therapy, or (6) treatment/therapy with ultraviolet light B (UVB).
 - e. Use within 8 weeks prior to baseline visit on trunk or extremities (1) 5-FU, (2) imiquimod, (3) diclofenac, or (4) photodynamic therapy or (5) other treatments for actinic keratosis within 2 cm of the selected treatment area.
 - f. Use of systemic retinoids within 6 months.
 - g. Known allergies to ingenol mebutate or any excipients in the test or reference product.
4. 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.
5. Subjects should not apply moisturizers, sun screen, make-up, creams, lotions, powders or any other over-the-counter topical products other than the assigned treatment to the treatment area for 15 days after treatment.
6. Subjects should avoid excessive sun exposure, use of tanning booths, sunlamps or nonprescription UV light sources or contact of the study drug in, around or near the eyes, lips or mouth.
7. 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 that might influence or mask the effects of treatment, such as 5-FU, imiquimod, diclofenac, topical salicylic acid, topical retinoids, bichloroacetic acid,

- trichloroacetic acid, cryodestruction, chemodestruction, surgical excision, CO₂ laser vaporization, electrocautery, photodynamic therapy, or curettage
- b. Immunomodulators or immunosuppressive therapies, cytotoxic drugs, interferon/interferon inducers or systemic steroids
 - c. Artificial tanner, psoralen plus ultraviolet A or ultraviolet B therapy, or excessive or prolonged exposure to ultraviolet lights source
 - d. Cosmetic or therapeutic procedures
 - e. Acid-containing therapeutic products
 - f. Medicated/therapeutic topical salves or topical steroids on trunk or extremities
8. The recommended primary endpoint of the study is the proportion of subjects with the per protocol (PP) population with treatment success (100% clearance of all AK lesions within the treatment area) at Day 57. 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.
9. Subjects are recommended to return to study site for investigator assessment on Day 3, 8, 15, 29 and 57 following treatment. If subjects have unresolved treatment emergent adverse events or local skin responses, site visits are recommended every 7 to 28 days until resolution or until investigator deemed clinically stable. Subjects with pigment related changes or scarring should return every 28 days until resolution or for a period of 6 months from Day 1 unless deemed by the investigator to be clinically insignificant.
10. Application site reactions such as erythema, flaking/scaling, crusting, swelling/edema, vesiculation/pustulation, erosion/ulceration, pigmentation, and scarring are to be recorded and scored at each visit using the scale: 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference product with regard to site reactions.
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>