

Contains Nonbinding Recommendations
Draft Guidance on Diclofenac Sodium

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Gel; topical

Recommended Studies: One study

1. Type of study: Bioequivalence Study with Clinical Endpoint
Design: Randomized, double blind, parallel, placebo controlled, in vivo
Strength: 3%
Subjects: Immunocompetent males and nonpregnant, nonlactating females with clinically typical, visible, non-hyperkeratotic, and nonhypertrophic actinic keratoses (AK) on the face or bald 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 study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends conducting a bioequivalence study with a clinical endpoint in the treatment of actinic keratoses (AK) of the face or bald scalp. Subjects are to be randomized to receive the diclofenac sodium 3% gel test product, the reference product, or placebo control. The study drug is to be applied twice daily for 60 days using enough gel to adequately cover each lesion. Generally, 0.5 gram of gel is used to cover one contiguous 25-cm² treatment area. Hand washing before and

after gel application is recommended. The primary endpoint is to be evaluated at Study Day 90 (30 days after completion of 60 days 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 ten (10) clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions, each at least 4 mm in diameter, contained within a 25-cm² treatment area located on the face or bald scalp.
3. Exclusion Criteria (the sponsor may add additional criteria)
 - a. Active gastrointestinal ulceration or bleeding.
 - b. Severe renal or hepatic impairment.
 - c. Presence of atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, sunburn or other possible confounding skin conditions on face or bald scalp.
 - d. Use within 6 months prior to randomization of oral isotretinoin.
 - e. Use within 6 months prior to randomization on the face or bald scalp of 1) chemical peel, 2) dermabrasion, 3) laser abrasion, 4) PUVA (psoralen plus ultraviolet A) therapy, or 5) UVB therapy.
 - f. Use within 1 month prior to randomization on the face or bald 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.
 - g. Use within 1 month prior to randomization of 1) immunomodulators or immunosuppressive therapies, 2) interferon, 3) oral corticosteroids or 4) cytotoxic drugs.
 - h. Known allergy or hypersensitivity to diclofenac, benzyl alcohol, polyethylene glycol monomethyl ether 359, hyaluronate sodium or other excipients in the test or reference product.
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, sun screen, creams, ointments, lotions, powders and new brands of make-up) applied on or near the treatment area.
 - b. Any therapy for AK, such as prescription topical retinoids, topical 5-fluorouracil, topical imiquimod, topical salicylic acid, bichloroacetic acid, trichloroacetic acid, cryodestruction, chemodestruction, surgical excision, CO₂ laser vaporization, electrocautery, photodynamic therapy, or curettage.
 - c. Immunomodulators or immunosuppressive therapies, interferon, oral corticosteroids, cytotoxic drugs, systemic corticosteroids, or topical steroids anywhere on the head.
 - d. Tanning booths, sun lamps, or nonprescription UV light sources.
 - e. The treated areas should not be bandaged, covered or wrapped as to be occlusive.
 - f. Subjects should be instructed to avoid exposure to sunlight, to not allow the gel to come in contact with the eyes, and to not apply the gel to open skin wounds, infections or exfoliative dermatitis.

5. 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 Day 90 (30 days after completion of 60 days 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.
6. 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
7. 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>