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Draft Guidance on Ingenol mebutate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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 (BE) with Clinical Endpoint Study
   Design: Randomized, double-blind, parallel, placebo-controlled, in vivo
   Strength: 0.05%
   Subjects: Healthy males and females (nonpregnant) 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): N/A

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: N/A

Dissolution test method and sampling times: N/A

Additional comments regarding the BE with clinical endpoint study:

1. The Office of Generic Drugs (OGD) recommends a BE 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 listed drug (RLD), or placebo. 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 cm^2 (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. A placebo (vehicle) control arm is recommended to demonstrate that the test product and RLD are active and as parameter to establish that the study is sufficiently sensitive to detect difference between products. It is especially important when studying a disease such as AK, in which spontaneous resolution may occur.

3. Inclusion criteria (the sponsor may add additional criteria):
   Healthy male or female (nonpregnant) at least 18 years of age with 4 to 8 clinically typical AK lesions, each at least 4 mm in diameter, within a contiguous 25 cm^2 treatment area located on the trunk or extremities.

4. 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 of (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, or (11) topical steroids.
    d. Use within 4 weeks of baseline visit on trunk or extremities of (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 week prior to baseline visit on trunk or extremities of (1) 5-FU, (2) imiquimod, (3) diclofenac, (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 product or RLD.

5. 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.

6. Subjects should not apply moisturizers, sunscreen, 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.

7. 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.

8. The protocol should include a list of the prescription and nonprescription/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, CO_2 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

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

10. 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.

11. The protocol should clearly define the PP, modified intent-to-treat (mITT) and safety populations.
    a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment, and completed the evaluation Day 57 within the designated visit window (+/- 2 days) with no protocol violations that would affect the treatment evaluation. The protocol should provide a definition of compliant subjects and specify how compliance will be verified (e.g., subjects to return medication tubes).
    b. The mITT population includes all randomized subjects who applied at least one dose of assigned product.
    c. The safety population includes all randomized subjects who received study product.

12. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of AK during the study should be discontinued, included in the PP population analysis as treatment failures, and provided with effective treatment. Subjects who are discontinued prematurely from the study due to lack of treatment effect should be included in the PP population as treatment failures (i.e., non-responders). Subjects discontinued prematurely for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).

13. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

14. 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.

15. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

16. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor must clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, and/or systemic or local availability of the drug.

17. The method of randomization should be described in the protocol and the randomization schedule provided as a SAS data set in .xpt format (created using SAS XPORT). It is recommended that an independent third party generate and hold the randomization code throughout the conduct of

the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity for each subject.

18. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

19. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples," regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline," for retention of study records and data in order to conduct their studies in compliance with good laboratory practices (GLP) and good clinical practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

20. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

21. To establish bioequivalence for the success rate (100% clearance of all AK lesions within the treatment area), it is recommended the following compound hypotheses be tested using the per protocol population:

    $$H_O: \pi_T - \pi_R \leq \Delta_1 \text{ or } \pi_T - \pi_R \geq \Delta_2 \text{ versus } H_A: \Delta_1 < \pi_T - \pi_R < \Delta_2$$

    where π_T = the success rate of the primary endpoint for the treatment group and
    π_R = the success rate of the primary endpoint for the reference group.

    The null hypothesis, H_O, is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test and reference products (π_T-π_R) is contained within the interval $[\Delta_1, \Delta_2]$, where Δ_1 = -0.20 and Δ_2 = 0.20. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

22. To establish sensitivity within the study, the test and reference product should both be statistically superior to the placebo. Conduct an appropriate inferential test for a dichotomous endpoint (success rate) with a type I error (α) of 0.05, using the mITT population and the primary endpoint.

23. Study data should be submitted to the OGD in electronic format. All data should be submitted as a SAS .xpt file, created using SAS XPORT (not CPORT).
    a. Include a list of file names, a description of the content of each file, an explanation of the variables within each file, and a description of all variable codes (for example, for the treatment variable, A = RLD and B = TEST).
    b. Provide a separate dataset for demographic, lesion count, vital sign, adverse event, disposition (including reason for discontinuation of treatment), concomitant medication, medical history, compliance, and comment variables.
    c. The methods used to derive the variables should be included and explained.

24. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Name of actual treatment (exposure): test product, RLD, placebo control
    i. Location of treatment area
    j. Duration of treatment (total exposure in days)
    k. Completed the study (yes/no)
    l. Reason for premature discontinuation of subject
    m. Subject required additional treatment for AK due to unsatisfactory treatment response (yes/no)
    n. Per Protocol (PP) population inclusion (yes/no)
    o. Reason for exclusion from PP population
    p. Modified Intent to Treat (mITT) population inclusion (yes/no)
    q. Reason for exclusion from mITT population
    r. Safety population inclusion (yes/no)
    s. Reason for exclusion from safety population
    t. Size of treatment area at baseline (cm^2)
    u. Total number of AK lesions in the treatment area at baseline
    v. Total number of AK lesions in the treatment area at Day 57
    w. Final designation as treatment success (100% clearance of all AK lesions within the treatment area) or failure
    x. Treatment compliance: number of missed doses per subject
    y. Concomitant medication (yes/no)
    z. Adverse event(s) reported (yes/no)

    Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs
101	1	01	54	YEARS	F	1	A	A	28	Y		N	Y		Y	
101	2	01	58	YEARS	F	1	B	B	28	Y		N	Y		Y	

safety	safetyrs	sizetrta	aksizeb	aknum_b	aknum57	naknum57	success	complian	CM	AE
Y		50	Y	4	2	0	Y	0	Y	Y
Y		40	Y	8	4	1	N	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/2008.

STUDYID:	Study identifier
SUBJID:	Subject identifier for the study
SITEID:	Study site identifier
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., M=male, F=female, U=unknown
RACE:	Race, e.g., 1=white, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or other Pacific Islanders
EXTRT:	Name of actual treatment (exposure), e.g., A=test product, B= RLD, C=placebo control
EXLOC:	Location of treatment area, e.g. A=arms, B=back, C=chest/abdomen, H=back of hands, L=legs, S=shoulder
EXDUR:	Duration of treatment (total exposure in days)
completd:	Subject completed the study, e.g., Y=yes, N=no
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt:	Subject required additional treatment for AK due to unsatisfactory treatment response, e.g., Y=yes, N=no
pp:	Per Protocol (PP) population inclusion, e.g., Y=yes, N=no
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt:	Modified Intent to Treat (ITT) population inclusion, e.g., Y=yes, N=no
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety:	Safety population inclusion, e.g., Y=yes, N=no
safetyrs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
sizetrta:	Size of treatment area at baseline (cm^2)
aksizeb:	Size of all AK lesions within treatment area at baseline are at least 4 mm in diameter, e.g., Y=yes, N=no
aknum_b:	Total number of AK lesions in the treatment area at baseline
aknum57:	Total number of AK lesions in the treatment area at Day 57
naknum57:	Total number of new AK lesions in the treatment area at Day 57
success:	Final designation, e.g., Y=yes (100% clearance of all AK lesions within the treatment area), N=no (failure)
complian:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, e.g., Y=yes, N=no
AE:	Adverse event(s) reported, e.g., Y=yes, N=no

25. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Name of actual treatment (exposure): test product, RLD, placebo control
    d. Location of dose administration: application site
    e. Visit number
    f. Visit date
    g. Number of days since baseline visit
    h. Evaluator: identity of evaluator
    i. Total number of AK lesions
    j. Total number of new AK lesions within treatment area
    k. Skin reaction scores for each sign and symptom evaluated (e.g., erythema, scaling, crusting, edema, erosion/ulceration, vesiculation/pustulation, pigmentation, scaring)
    l. Concomitant medication reported during this visit (yes/no)
    m. Adverse event reported during this visit (yes/no)
    n. Laboratory testing during this visit (yes/no)

    Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of dataset containing one line listing for each visit per subject

STUDYID	**SUBJID**	**EXTRT**	**EXLOC**	**VISITNUM**	**SVSTDTC**	**ELTMBS**	**EVAL**	**aknum**	**naknum**	**erythema**	**scaling**	**crusting**	**edema**	**erosion**	**vesiculation**	**pigmentation**	**scaring**	**CMrpt**	**AErpt**	**LBtest**
101	1	A	A	1	2004-07-01	1	JB	7	1	1	0	0	1	0	0	0	1	Y	Y	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/2008.

STUDYID:	Study identifier
SUBJID:	Subject identifier for the study
EXTRT:	Name of actual treatment (exposure), e.g. A=test product, B=RLD, C= placebo control
EXLOC:	Location of treatment area: specific anatomical site of application, e.g., A=arms, B=back, C=chest/abdomen, H=back of hands, L=legs, S=shoulder
VISITNUM:	Visit sequence number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed time since baseline (days)
EVAL:	Evaluator: identity of the evaluator
aknum:	Total number of AK lesions within treatment area
naknum:	Total number of new AK lesions within treatment area
erythema:	Skin reaction erythema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

scaling:	Skin reaction scaling score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
crusting:	Skin reaction crusting score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3-severe (marked, intense)
edema:	Skin reaction edema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
erosion:	Skin reaction erosion score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
vesiculation:	Skin reaction vesiculation score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
pigmentation:	Skin reaction pigmentation score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
scaring:	Skin reaction scaring score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
CMrpt:	Concomitant medication reported during this visit, e.g., Y=yes, N=no
AErpt:	Adverse event reported during this visit, e.g., Y=yes, N=no
LBtest:	Laboratory testing performed during this visit, e.g., Y=yes, N=no

26. The study data should be submitted in standardized format. Consider the implementation and use of data standards as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis stages of clinical studies. For more details, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

27. The protocol should include a full detailed statistical analysis plan and describe how missing data will be prevented and handled if exist.

28. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of ingenol mebutate.