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Draft – Not for Implementation

Draft Guidance on Mechlorethamine Hydrochloride

February 2023

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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: Mechlorethamine hydrochloride

Dosage Form; Route: Gel; topical

Recommended Studies: Two options: (1) one in vitro bioequivalence study and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

I. Option 1: One in vitro bioequivalence study and other characterization tests

To demonstrate bioequivalence for mechlorethamine hydrochloride topical gel, EQ 0.016% Base using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and reference standard are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*[a], and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

2. The test product and reference standard should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the test product and three batches (as available) of the reference standard. The test product and reference standard batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional

information regarding comparative Q3 characterization tests. The comparison of the test product and reference standard should include characterizations of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    - Analysis of particle size distribution, crystal habit, and polymorphic form of mechlorethamine hydrochloride in the drug product, if applicable
c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
    - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
d. Characterization of specific gravity
e. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard should have an equivalent rate of mechlorethamine hydrochloride release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the test product and reference standard using an appropriately validated IVRT method.

    Type of study: Bioequivalence study with IVRT endpoint
    Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
    Strength: EQ 0.016% Base
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Mechlorethamine in receptor solution
    Equivalence based on: Mechlorethamine (IVRT endpoint: drug release rate)
    Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and reference standard evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

II. Option 2: One in vivo bioequivalence study with clinical endpoint

1. Type of study: Bioequivalence study with clinical endpoint
    Design: Randomized, double-blind (evaluator-blinded), parallel, two-arm, in vivo study
    Strength: EQ 0.016% Base
    Subjects: Male and female patients with Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL; MF)

Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. Submission of an Investigational New Drug Application (IND) is required prior to conducting a bioequivalence study for a cytotoxic drug product such as mechlorethamine (see 21 C.F.R § 320.31).

2. FDA recommends conducting a bioequivalence study with a clinical endpoint in the treatment of Stage IA and IB MF, comparing the test product versus the reference standard. Patients are to be randomized to receive the test mechlorethamine hydrochloride topical gel, EQ 0.016% Base and the reference standard mechlorethamine hydrochloride topical gel, EQ 0.016% Base, and stratified based on disease stage and duration. The study drug is applied once daily on affected areas of the skin. The primary endpoint is overall clinical response including complete or partial response determined by the Composite Assessment of Index Lesion Disease Severity (CAILS) in patients who have completed treatment for 6 months.

3. Inclusion criteria (the sponsor may add additional criteria):
    a. Male or non-pregnant, non-lactating females (18 years or older)
    b. A diagnosis of stage IA or IB MF histologically confirmed by a skin biopsy
    c. Patients who have received prior skin-directed therapy (e.g., therapies with psoralen plus ultraviolet A (PUVA), ultraviolet A (UVA) or topical steroids)

4. Exclusion criteria (the sponsor may add additional criteria):
    a. Newly diagnosed MF with no prior therapy
    b. A prior history of treatment with topical nitrogen mustard or carmustine products
    c. Use of topical or systemic therapies for MF within four weeks prior to the study
    d. Patients with a diagnosis of Stage II-IV MF
    e. Patients who have had radiation therapy within one year prior to the study
    f. Females who are pregnant, breast feeding, planning a pregnancy
    g. Males and females of childbearing potential who do not agree to use effective contraception throughout the study
    h. Concurrent chronic medical conditions which could potentially present a safety risk and/or prevent compliance with the requirements of the treatment program

5. The protocol should include a list of the prescription and nonprescription/over-the-counter drug products, procedures, and activities that are prohibited during the study, such as: any topical or systemic therapies (e.g., PUVA, UVB, steroids, radiation and bexarotene) to treat MF other than the products for the study. Topical steroids (up to 1%) may be permitted for non-MF lesions.

6. Subjects or care givers should be instructed for proper application and storage of the product. The product should be applied to completely dry skin at least 4 hours before or 30 minutes after showering or washing and allow treated areas to dry for 5 to 10 minutes after application before covering with clothing. Occlusive (air or water-tight) dressings should not be used on areas of the skin where the product has been applied.

7. Moisturizers may be applied to the treated areas 2 hours before or 2 hours after application of the product.

8. Exposure to mucous membranes, especially of the eyes or the oral or nasal mucosa, should be avoided and, if mucosal contact occurs, it should be immediately irrigated with copious amounts of water and then contact the investigator for medical consultation.

9. Patients should avoid direct contact and unintentional exposure to other people to prevent secondary exposure. Patients must wash hands thoroughly with soap and water after handling or applying the product. If caregivers apply the product to patients, they must wear disposable nitrile gloves and wash hands thoroughly with soap and water after removal of gloves.

10. Temporary or permanent treatment discontinuation should be considered for patients who show any treatment-limiting adverse reactions including dermal irritation. Criteria for terminating treatment and application method for resuming treatments should be described in the protocol.

11. The primary endpoint is an overall response, defined as complete response or partial response using CAILS score, in patients who have completed 6 months of treatment. Index lesions for CAILS score (up to a maximum of 5 MF lesions) should be designated at baseline (the start of treatment). Index lesions should be separate and distinct from other lesions to minimize the chance for lesion confluence. If the patient has 5 or fewer lesions, all lesions should be designated as index lesions. The assessment for the response should be performed by two or more consecutive observations over at least 4 weeks after completing the treatment for 6 months.

    The response in skin of patients with MF can use the following criteria:

Complete response (CR)	100% clearance of skin lesions; CAILS score of 0
Partial response (PR)	≥ 50% clearance of skin disease; CAILS score of ≥ 50% reduction from baseline
Stable disease (SD)	< 25% increase to < 50% clearance in skin disease; CAILS score of < 50% reduction from baseline
Progressive disease (PD)	≥ 25% increase in skin disease: CAILS score of ≥ 25% increase from baseline

12. Investigators should monitor for treatment-limiting adverse reactions throughout the study and treatment response monthly. After completing the study, all patients should be followed up for continuing treatment using the reference standard or alternative therapy and (or) continuing clinical evaluation by investigators or their health care providers.

13. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
    a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who:
        - Meet all inclusion/exclusion criteria.
        - Are dosed a pre-specified proportion of the scheduled doses (Generally At least 75% and no more than 125%) of the assigned product for the specified duration of the study. The protocol should specify how compliance will be verified, (e.g., by the use of subject diaries).
        - Do not miss a pre-specified number of scheduled doses for more than pre-specified number of consecutive days.
        - Complete the evaluation within the designated visit window with no protocol violations that would affect the treatment evaluation.
    b. The mITT and safety populations include all randomized subjects who use at least one dose of product.

14. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population using Last Observation Carried Forward (LOCF). Subjects whose condition worsens and who require alternate or supplemental therapy for the treatment of their condition during the treatment phase of the study should be discontinued, included in the mITT and PP population analyses using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF. Applicants should provide a pre-specified definition of lack of treatment effect.

15. The start and stop calendar date (e.g., mm/dd/yyyy) and study day (e.g., Day X) of concomitant medication use should be provided in the data set in addition to the reason for the medication use. The Applicant should clearly note whether the medication was used prior to baseline visit, during the study, or both.

16. 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, action taken, outcome 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.

17. All pregnancies should be reported, including outcome information.

18. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the Applicant is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy, or systemic or

local availability of the drug. Inactive ingredients used should provide adequate margins of safety for the proposed clinical exposure in the target population (e.g., 2 months and older).

19. The method of randomization should be described in the protocol and the randomization schedule should be provided. 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 Applicant 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 of each subject.

20. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test product and reference standard 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.

21. Refer to 21 CFR 320.38, 320.63 and the most recent version of the FDA guidance for industry on, "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 for each shipment prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.

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

23. To establish bioequivalence for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

    $H_O: \pi_T - \pi_R < \Delta_1$ or $\pi_T - \pi_R > \Delta_2$ versus $H_A: \Delta_1 \leq \pi_T - \pi_R \leq \Delta_2$

    where π_T = the success rate of the primary endpoint for the test product group, and
    π_R = the success rate of the primary endpoint for the reference standard 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 product and reference standard ($\pi_T - \pi_R$) is contained within the interval $[\Delta_1, \Delta_2]$, where Δ_1 and Δ_2 should be based on the treatment effect size of the reference standard

calculated using a meta-analysis of past studies conducted in a similar patient population and under similar conditions. The justification for the choice of Δ_1 and Δ_2 should be provided in the IND. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

24. The protocol should include a section with fully detailed statistical analysis plan.

25. Provide the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Name of actual treatment
    j. Name of planned treatment
    k. Safety population flag (yes/no)
    l. Reason for exclusion from safety population
    m. Modified Intent-to-Treat (mITT) population flag (yes/no)
    n. Reason for exclusion from mITT population
    o. Per-Protocol (PP) population flag (yes/no)
    p. Reason for exclusion from PP population
    q. Randomized population flag (yes/no)
    r. Date/time of first exposure to treatment
    s. Date/time of last exposure to treatment
    t. End of study date
    u. End of study status
    v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
    w. Duration of treatment (total exposure in days)
    x. Completed the study (yes/no)
    y. Reason for premature discontinuation of subject
    z. Subject required permanent discontinuation of the treatment (yes/no)
    aa. Subject required temporary suspension and resumption of the treatment (yes/no)
    bb. The number of skin lesions treated
    cc. The number of index skin lesions for CAILS score
    dd. Baseline CAILS score
    ee. CAILS score after completing the treatment of 6-month
    ff. Clinical response based on CAILS score
    gg. Compliance rate (%)
    hh. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
    ii. Adverse event reported (yes/no)

jj. Concomitant medication (yes/no)

26. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier for the study
    d. Study site identifier (if applicable)
    e. Name of planned treatment
    f. Name of actual treatment
    g. Safety population flag (yes/no)
    h. Modified ITT population flag (yes/no)
    i. Per-Protocol (PP) population flag (yes/no)
    j. Analysis date
    k. Analysis visit
    l. Study visit within the designated window (yes/no)
    m. Analysis timepoint (e.g., hour 0, hour 2) (if applicable)
    n. Number of days since baseline visit
    o. The number of skin lesions treated
    p. The number of index skin lesions
    q. CAILS score
    r. Clinical response based on CAILS score
    s. Additional treatment required during the visit (yes/no)
    t. Adverse event reported during the visit (yes/no)
    u. Concomitant medication reported during this visit (yes/no)

27. Refer to the study data standards resources, https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

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[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.