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Draft Guidance on Mupirocin Calcium

October 2022

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Active Ingredient: Mupirocin calcium

Dosage Form; Route: Cream; 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 mupirocin calcium topical cream, EQ 2% 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 in the same packaging configuration (tube or pump) 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 in the same packaging configuration (tube or pump) 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 mupirocin calcium in the drug product
    - Analysis of globule size distribution
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).
    - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
    - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
d. Characterization of water activity and drying rate
e. Characterization of pH
f. Characterization of specific gravity
g. Characterization of any other potentially relevant Q3 attributes

3. The test product and reference standard in the same packaging configuration (tube or pump) should have an equivalent rate of mupirocin calcium 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 2% Base
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Mupirocin in receptor solution
    Equivalence based on**:** Mupirocin (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, parallel, placebo controlled, in vivo
   Strength: EQ 2% Base
   Subjects: Healthy males and non-pregnant females with secondarily infected traumatic skin lesion
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends conducting a clinical endpoint bioequivalence study in the treatment of secondarily infected traumatic skin lesions. Subjects are to be randomized to receive the test mupirocin calcium topical cream, EQ 2% base, the reference standard, or placebo vehicle applied to the affected area three times daily for 10 days. The primary endpoint is the proportion of subjects with clinical cure at 7 days after the end of treatment (Study Day 17).

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Male or non-pregnant, non-lactating female aged ≥ 18 months with a secondarily infected traumatic skin lesion(s) such as a laceration, sutured wound or abrasion. The laceration or sutured wound should not exceed 10 cm in length with surrounding erythema not more than 2 cm from the edge of the lesion. An abrasion should not exceed 100 cm^2 in total area with surrounding erythema not more than 2 cm from the edge of the abrasion.
   b. Positive baseline culture for *Staphylococcus aureus* and/or *Streptococcus pyogenes* from a sample taken from the secondarily infected traumatic skin lesion.
   c. Positive Gram stain or Wright stain for confirmation of white blood cells in the pus/exudate from the secondarily infected traumatic skin lesion.
   d. Skin Infection Rating Scale (SIRS) total score for the secondarily infected traumatic skin lesion of at least 8 at baseline (per Table 1).

Table 1. Sample SIRS

Sign/symptom	Score	Definition
Exudate/pus	0=Absent 1=Mild 2=Moderate 3=Severe	No evidence of exudate or pus Small amount of fluid/pus coming from the skin lesion(s) Exudate/pus infected area is moderate Extensive area of skin lesion is infected and there is draining exudate
Crusting	0=Absent 1=Mild 2=Moderate	No evidence of crusting A few areas have some evidence of crusting lesions Crusting is present throughout the infected area

	3=Severe	Thick crusting appears over the entire infected area
Erythema/ inflammation	0=Absent 1=Mild 2=Moderate 3=Severe	Skin tone and color are normal; no signs of erythema or inflammation Skin is pink with minimal signs of inflammation Skin is red with definite signs of inflammation Skin is red and severe inflammation is present
Tissue edema	0=Absent 1=Mild 2=Moderate 3=Severe	No evidence of tissue edema Tissue has mild edema Tissue has moderate edema Tissue has severe edema
Tissue warmth	0=Absent 1=Mild 2=Moderate 3=Severe	No evidence of tissue warmth Tissue has mild warmth Tissue has moderate warmth Tissue has severe warmth
Itching	0=Absent 1=Mild 2=Moderate 3=Severe	No itching Some evidence of scratching or rubbing the area is evident and subject reports minor discomfort Evidence of scratching and subject reports bothersome itching Evidence of extensive scratching and subject reports itching interferes with daily activities or sleep
Pain	0=Absent 1=Mild 2=Moderate 3=Severe	No pain Slight pain; not bothersome; no analgesics being taken Definite pain; subject reports bothersome pain, without loss of sleep, mild analgesic may be taken Intense pain that that interferes with daily activities or sleep; medication required to control pain

3. Exclusion Criteria (the sponsor may add additional criteria):
    a. Females who are pregnant, breast feeding, or who wish to become pregnant during the study period.
    b. Any dermatological disorder that may interfere with the evaluation of the subject's secondarily infected traumatic skin lesion(s), e.g., acute or chronic dermatitis involving affected area.
    c. Bacterial skin infection which, due to depth of severity, could not be appropriately treated by a topical antibiotic (e.g., severe cellulitis, abscess, ulcers, furunculosis).
    d. Secondarily infected animal/human or insect bite or puncture wound.
    e. Systemic sign and symptoms of infection (i.e., fever defined as an oral. temperature greater than 101°F or 38.3°C).
    f. Require surgical intervention for treatment of the infection prior to enrollment in the study.
    g. Use within 1 week prior to baseline of systemic antibiotic or systemic corticosteroid.

h. Use within 48 hours prior to baseline of topical corticosteroid, topical antibiotic, or antifungal.
i. Primary or secondary immunodeficiency.
j. Diabetes.
k. Presence of any other medical condition that might adversely impact the safety of the study participants or confound the study results.
l. History of hypersensitivity or allergy to mupirocin and/or any of the study medication ingredients.

4. The study protocol should include early observation of the subjects (i.e., on Study Day 3) and provision for switching to an approved treatment (e.g., Bactroban® or oral therapy) if the subject is not improving. These subjects should be discontinued and analyzed as treatment failures.

5. 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. Any other topical products (including antibacterial soaps) applied on or near the affected area
    b. Systemic (e.g., oral or injectable) antibiotics
    c. Systemic corticosteroids or immunosuppressive drugs

6. The recommended primary endpoint is the proportion of subjects in each treatment group with clinical cure (defined as a SIRS score of 0 for all signs and symptoms on a 4-point scale provided in Comment #2 above) at the Day 17 follow-up visit (7 days after the end of treatment).

7. The proportion of subjects with clinical cure at the end of treatment visit, bacteriological cure (defined as elimination of *Staphylococcus aureus* and *Streptococcus pyogenes* or response was such that no culture material was available and therefore evidence of pathogen eradication) at the end of treatment visit, and bacteriological cure at the follow-up visit should be treated as secondary endpoints for supportive evidence.

8. Subjects with a negative culture at baseline should be discontinued from the study and excluded from the modified intent-to-treat (mITT) and per-protocol (PP) populations but included in the ITT population for safety analysis.

9. The type of skin lesion, size of treatment area and site of treatment area should be compared and tabulated for each treatment group.

10. 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 planned treatment
j. Name of actual treatment
k. Safety population flag (yes/no)
l. Reason for exclusion from safety population
m. mITT population flag (yes/no)
n. Reason for exclusion from mITT population
o. PP population flag (yes/no)
p. Reason for exclusion from PP population
q. Randomized population flag (yes/no)
r. Type of secondarily infected traumatic skin lesion (e.g., laceration, abrasion, suture)
s. Size of Treatment Area (e.g., cm^2)
t. Date/time of second exposure to treatment
u. Location of Treatment Area
v. Duration of Treatment (total exposure in days)
w. End of study date
x. Completed the study (yes/no)
y. Reason for premature discontinuation of subject
z. Subject required additional treatment for their secondarily infected traumatic skin lesion due to unsatisfactory treatment response (yes/no)
aa. Clinical outcome (cure/failure)
bb. Compliance rate (%)
cc. Adverse event reported (yes/no)
dd. Concomitant medication (yes/no)

11. 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. Location of Dose Administration: application site
    h. Safety population flag (yes/no)
    i. Modified ITT population flag (yes/no)
    j. PP population flag (yes/no)
    k. Analysis date
    l. Number of days since baseline visit
    m. Analysis visit
    n. Evaluator: identity of evaluator
    o. Individual exudate/pus SIRS score
    p. Individual crusting SIRS score
    q. Study visit within the designated window (yes/no)

r. Individual erythema/inflammation SIRS score
s. Individual tissue edema SIRS score
t. Individual tissue warmth SIRS score
u. Individual itching SIRS score
v. Individual pain SIRS score
w. Total SIRS score
x. White blood cells identified on Gram stain or Wright stain (yes/no)
y. Bacterial cure (yes/no)
z. Culture results
aa. Clinical cure (yes/no)
bb. Additional treatment required during the visit (yes/no)
cc. Adverse event reported during the visit (yes/no)
dd. Concomitant medication during the visit (yes/no)

12. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for BE studies with clinical endpoint.

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

Revision History: Recommended June 2010; Revised October 2011, October 2022

Unique Agency Identifier: PSG_050746

[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.
[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance web page at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.