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Draft Guidance on Metronidazole

October 2022

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Active Ingredient: Metronidazole

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 metronidazole topical gel, 1% 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
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.
d. Characterization of pH
e. Characterization of specific gravity
f. 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 metronidazole 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: 1%
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Metronidazole in receptor solution
    Equivalence based on**:** Metronidazole (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: 1%
   Subjects: Males and non-pregnant, non-lactating females with rosacea
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. FDA recommends a bioequivalence study with clinical endpoint in the treatment of moderate to severe rosacea. Subjects are to be randomized to receive the test metronidazole topical gel, 1%, the reference standard, or placebo once daily for 10 weeks. The primary endpoint is to be evaluated at the end of treatment (Study Week 10).

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Male or non-pregnant, non-lactating female aged ≥ 18 years with a clinical diagnosis of moderate to severe facial rosacea, defined as the presence of all of the following:
      i. A total of 8 to 50 combined papules/pustules on the face
      ii. At least moderate erythema
      iii. Telangiectasia
   b. Subject willing to minimize external factors that might trigger rosacea flare-ups (e.g., spicy foods, thermally hot foods and drinks, hot environments, prolonged sun exposure, strong winds and alcoholic beverages)

3. Exclusion Criteria (the sponsor may add additional criteria):
   a. Pregnant or lactating or planning to become pregnant during the study period.
   b. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea.
   c. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea.
   d. History of hypersensitivity or allergy to metronidazole, or other ingredients of the formulation.
   e. Use within 6 months prior to baseline of oral retinoids (e.g., Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
   f. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.
   g. Use within 1 month prior to baseline of 1) topical retinoids to the face, 2) systemic antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline and its derivatives, erythromycin and its derivatives, sulfamethoxazole, or trimethoprim), or 3) systemic steroids.
   h. Use within 2 weeks prior to baseline of 1) topical corticosteroids, 2) topical antibiotics or 3) topical medications for rosacea (e.g., metronidazole, azelaic acid).

i. Current use of anticoagulation therapy.
j. History of blood dyscrasia.
k. Ocular rosacea (e.g., conjunctivitis, blepharitis, or keratitis) of sufficient severity to require topical or systemic antibiotics.

4. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
    a. Any anticoagulation therapy
    b. Any other topical products applied to the target site (e.g., azelaic acid, topical antibiotics, topical steroids)
    c. Oral retinoids
    d. Systemic (e.g., oral or injectable) antibiotics known to have an impact on the severity of facial rosacea (e.g., containing tetracycline, erythromycin, sulfamethoxazole, or trimethoprim or their derivatives)
    e. Systemic corticosteroid or immunosuppressive drugs
    f. Antipruritics, including antihistamines, within 24 hours of study visits

5. Subjects should not apply moisturizers, new brands of make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Subjects should minimize exposure to sunlight, including sunlamps, while using the product. Use of sunscreen products and protective clothing over treated areas is recommended when sun exposure cannot be avoided.

6. Areas to be treated should be washed with a mild cleanser before application. Subjects are to apply and rub in a thin layer of study treatment once daily, in the morning and evening, to entire affected areas for 10 weeks. Contact with the eyes should be avoided.

7. The recommended primary endpoint of the study is the mean percent change from baseline to Week 10 in the inflammatory (papules and pustules) lesion counts of rosacea. The protocol should clearly define papules, pustules, and nodules. When counting facial lesions, it is important that all lesions be counted, including those present on the nose. Counts of nodules should be reported separately and not included in the inflammatory lesion counts.

8. 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 bioequivalence studies with clinical endpoint.

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

Revision History: Recommended March 2010; Revised September 2019, October 2022

Unique Agency Identifier: PSG_021789

[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.