Contains Nonbinding Recommendations

Draft Guidance on Metronidazole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: in vitro or in vivo study

1. In vitro option:

To qualify for the in vitro option to demonstrate bioequivalence for metronidazole topical cream, 0.75% the following criteria should be met:

A. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient. For example, if the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*[1], with allowance for the amount of a pH modifier utilized to match the pH of the reference product the bioequivalence of the test product with respect to the reference product may be established using the in vitro option if the criteria below are also satisfied.

B. The test and reference products should be physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three batches of the test and three batches (as available) of the reference product. The characterization of the test and reference products should include the following comparisons of physical and structural attributes between the test and reference products:

   i. Assessment of visual appearance with representative microscopic images at multiple magnifications.

   ii. Characterization of the globule size distribution of the emulsion.

   iii. Analysis of the 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:

[1] The current version of the referenced guidance at the time of publication of this product specific guidance is Guidance for Industry: ANDA Submissions – Refuse-to-Receive Standards, Revision 2 (December 2016). However, we update guidances periodically, and current information related to guidances is maintained at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- A characterization of shear stress and viscosity vs shear rate. At minimum this should consist of numerical viscosity data at three shear rates (low, medium, and high), and may include 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.

iv. Analysis of pH, specific gravity, and any other potentially relevant physical and structural attributes.

C. The test and reference products should have an equivalent rate of metronidazole release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVRT method. Refer to the *Draft Guidance on Acyclovir* (for acyclovir topical cream, 5%)[2] for additional information regarding the development, validation, conduct, and analysis of acceptable IVRT methods/studies. The batches of test and reference products evaluated in the IVRT study should be included among those for which the physical and structural similarity is characterized and compared.

D. The test and reference products should have an equivalent rate and extent of metronidazole permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVPT method. Refer to the *Draft Guidance on Acyclovir* (for acyclovir topical cream, 5%)[2] for additional information regarding the development, validation, conduct, and analysis of acceptable IVPT methods/studies. The batches of test and reference products evaluated in the IVPT study should be the same as those evaluated in the IVRT study.

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2. In vivo option:

Type of study: Clinical Endpoint Bioequivalence Study
Design: Randomized, double blind, parallel, placebo controlled in vivo
Strength: 0.75%
Subjects: Males and nonpregnant, nonlactating females with rosacea
Additional comments: Specific recommendations are provided below

[2] The current version of the referenced guidance at the time of publication of this product specific guidance is Draft Guidance on Acyclovir for acyclovir topical cream, 5% (recommended Dec 2014; revised Dec 2016). However, we update guidances periodically, and current information related to product specific guidances is maintained at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm.

Analytes to measure (in appropriate biological fluid): Not applicable

Bioequivalence based on (90% CI): See additional comments below for the bioequivalence study with clinical endpoint

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Additional comments regarding the clinical endpoint bioequivalence study:

1. The Office of Generic Drugs (OGD) recommends a clinical endpoint bioequivalence study in the treatment of moderate to severe rosacea. Subjects are to be randomized to receive the generic metronidazole topical cream, 0.75%, the reference product, or placebo twice daily for 12 weeks. The primary endpoint is to be evaluated at the end of treatment (Study Week 12).

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Male or nonpregnant female aged ≥ 18 years with a clinical diagnosis of moderate to severe facial rosacea, defined as the presence of:
      i. A total of 8 to 50 combined papules/pustules on the face, AND
      ii. At least moderate erythema, AND
      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 twice daily, in the morning and evening, to entire affected areas for 12 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 12 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 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.[3]

9. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov[4]

[3] Product-Specific Guidances for Generic Drug Development available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

[4] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm