

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Minocycline Hydrochloride

November 2021

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

This is a new draft product-specific guidance for industry on generic minocycline hydrochloride.

Active Ingredient: Minocycline hydrochloride

Dosage Form; Route: Aerosol, foam; topical

Recommended Study: One study

1. Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double blind, parallel, placebo controlled, in vivo
Strength: EQ 1.5% Base
Subjects: Males and non-pregnant, non-lactating females with rosacea
Additional comments: Specific recommendations are provided below

Analyte to measure: Not applicable

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development* and the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. The FDA recommends a clinical endpoint bioequivalence study in the treatment of rosacea. Subjects are to be randomized to receive the test product, the reference product, or placebo once 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, nonlactating female aged ≥ 18 years with a clinical diagnosis of moderate to severe facial rosacea, defined as follows:
 - At least 15 and not more than 75 facial inflammatory facial lesions (i.e., papules/pustules)
 - No more than 2 nodules on the face
 - 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. Presence of any skin condition on the face that would interfere with the diagnosis or assessment of rosacea
 - b. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of rosacea
 - c. History of hypersensitivity or allergy to minocycline, any other tetracycline, or any other component of the formulation
 - d. 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)
 - e. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.
 - f. Use within 1 month prior to baseline of
 - Topical retinoids to the face
 - 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)
 - Systemic corticosteroids

- g. Use within 2 weeks prior to baseline of
 - Topical corticosteroids
 - Topical antibiotics
 - Topical medications for rosacea (e.g., metronidazole, azelaic acid)
 - h. Subjects with moderate or severe rhinophyma, dense telangiectasia, or plaque-like facial edema
 - i. 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 other topical products applied to the target site (e.g., metronidazole, topical antibiotics, topical steroids)
 - b. Oral retinoids
 - c. 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)
 - d. Systemic corticosteroid or immunosuppressive drugs
 - e. Antipruritics, including antihistamines, within 24 hours of study visits
5. Subjects should not apply new brands of make-up, moisturizer, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Occlusive dressings or wrappings should be avoided in treatment areas. 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 and patted dry with a soft towel. Study treatment should be applied to the entire facial area (cheeks, chin, forehead, and nose) at about the same time each day, at least 1 hour before bedtime, for 12 weeks. Contact with the mouth, eyes and other mucous membranes should be avoided. The hands should be washed following application. Subjects should not bathe, shower, or swim for at least 1 hour after applying study treatment.
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. 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 draft product-specific guidance on *Adapalene; Benzoyl Peroxide, Gel; Topical, 0.3%; 2.5%* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoint.

9. Study data should be submitted in a standardized format. Refer to the study standards published at www.fda.gov.¹

Additional information

Device:

This product is a drug-device combination product. Refer to the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*. An ANDA for a proposed generic drug-device combination product should include complete comparative analyses.

Unique Agency Identifier: PSG_213690

¹ Study Data Standards Resources: <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>