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Draft Guidance on Metronidazole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Recommended Studies: Two options: (1) in vitro studies or (2) in vivo studies

1. Option 1: In vitro studies

To qualify for the in vitro option to demonstrate bioequivalence for metronidazole vaginal gel, 1.3% 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 and the criteria below are also satisfied, the bioequivalence of the test product with respect to the reference product may be established using a characterization-based bioequivalence approach.

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 product and three batches (as available) of the reference product. The comparison of the test and reference products should include characterizations of the following physical and structural attributes:

   i. Assessment of visual appearance.

   ii. Microscopic examination with representative high-resolution microscopic images at multiple magnifications.

   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 Guidance for industry ANDA Submissions – Refuse-to-Receive Standards
• A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At a 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 (when possible).

• Yield stress values should be reported if the material tested exhibits plastic flow behavior.

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. The IVRT study should be conducted at 37°C based on the route of administration of this drug product. 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. Refer to the Guidance on Acyclovir (for acyclovir topical cream, 5%) for additional information regarding the development, validation, conduct and analysis of IVRT methods/studies.

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

Bioequivalence based on (90% CI): Refer to the Guidance on Acyclovir (for acyclovir topical cream, 5%) for additional information regarding the analysis of in vitro studies.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

2. Option 2: In vivo studies

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-way crossover, in vivo
   Strength: 1.3% [dose: one applicator full (5 grams containing approximately 65 mg of metronidazole in the to-be-marketed or currently marketed applicator provided with the product), administered intravaginally]
   Subjects: Nonpregnant, nonlactating females, general population
   Additional comments: No sexual intercourse or use of spermicides, tampons, douches, diaphragms, or condoms or insertion into the vagina of any drug or non-drug product are permitted within 48 hours of dosing. Exclude subjects with any vulvar or vaginal

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2 Guidance on Acyclovir for acyclovir topical cream, 5%
condition that may affect drug absorption (e.g., vulvovaginitis). Measure applicator weight after filling and after dosing to calculate weight of dose. Subjects should remain supine for at least 4 hours after dosing.

2. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double blind, parallel, placebo-controlled, in vivo
   Strength: 1.3%
   Subjects: Nonpregnant, nonlactating females with bacterial vaginosis
   Additional comments: Specific recommendations are provided below.

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**Analytes to measure (in appropriate biological fluid):** Metronidazole in plasma

**Bioequivalence based on (90% CI):** Metronidazole in plasma (pharmacokinetic study); clinical endpoint

**Waiver request of in vivo testing:** Not applicable

**Dissolution test method and sampling times:** Not applicable

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**Additional comments regarding the bioequivalence study with clinical endpoint:**

1. The Office of Generic Drugs recommends a bioequivalence study with clinical endpoint in the treatment of non-pregnant female subjects with a confirmed clinical diagnosis of bacterial vaginosis (BV). Subjects are to be randomized to receive the generic metronidazole vaginal gel, 1.3%, the reference product, or placebo as one applicator full (approximately 5 grams containing approximately 65 mg of metronidazole in the to-be-marketed or currently marketed applicator provided with the product) administered intravaginally once at bedtime.

2. Inclusion Criteria (the sponsor may add additional criteria):
   a. Nonpregnant, nonlactating female age ≥ 18 years.
   b. Diagnosis of bacterial vaginosis, defined as the presence of all of the following:
      i. Clinical diagnosis of bacterial vaginosis (e.g., off-white or gray, thin, homogenous vaginal discharge associated with minimal or absent pruritus inflammation AND
      ii. Saline wet mount of vaginal discharge demonstrating the proportion of clue cells to be ≥ 20% of the total epithelial cells AND
      iii. Vaginal pH > 4.5, using pH paper that measures from 4.0-6.0 AND
      iv. Positive “whiff test” (after addition of a drop of 10% KOH to vaginal discharge) AND
      v. Gram stain Nugent score ≥ 7 on first day of dosing (study Day 1)
   c. Any subject with childbearing potential has a negative urine pregnancy test on the first day of dosing (study Day 1) using a pregnancy test with a sensitivity of at least 25 mIU/mL hCG.
d. Willing to refrain from using any intra-vaginal product or device other than the study treatment (e.g., other vaginal drugs, spermicide, tampon, douche, diaphragm, condom, or other objects) on study days when study treatment is administered, for 48 hours prior to the dose of study product, and for 48 hours prior to Test of Cure visit.

e. Agrees to abstain from sexual intercourse on study days when study treatment is administered.

f. Willing to refrain from alcohol ingestion on study Days 1-2.

3. Exclusion Criteria (the sponsor may add additional criteria):
   a. Pregnant, lactating, or planning to become pregnant during the study period.
   b. Menstruating at the Baseline visit (when evaluation for BV is performed) or anticipate onset of menses during study drug administration.
   c. Primary or secondary immunodeficiency.
   d. Severe liver disease.
   e. Central nervous system disease.
   f. Evidence of any vulvovaginitis other than BV (e.g., candidiasis, Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae, Herpes simplex, or human papilloma virus).
   g. Subject with another vaginal or vulvar condition, which would confound the interpretation of clinical response.
   h. Subject will be under treatment during the study period for cervical intraepithelial neoplasia or cervical carcinoma.
   i. History of hypersensitivity or allergy to metronidazole, parabens, other nitroimidazole derivatives or other ingredients of the formulation.
   j. Use of any of the following medications within 2 weeks of the Baseline visit:
      i. Systemic steroids (oral or injectable)
      ii. Disulfiram
      iii. Lithium
      iv. Topical or systemic antibiotics
      v. Topical or systemic antifungal
      vi. Topical or systemic antiparasitic
   k. Use of intra-vaginal product or device (e.g., other vaginally administered drugs, spermicide, tampon, douche, diaphragm, condom, other objects) within 48 hours of study Day 1 dosing.
   l. Current use of anticoagulation therapy or cimetidine.

4. At the Baseline visit, documentation of the participant’s medical history should include menopausal status. For postmenopausal women, document the month and year of the last menses. For premenopausal women, documented information should include: the first day of the last menstrual period, regularity of menses, use of contraception, past episodes of BV, and sexual history (e.g., sex of intimate partners and history of sexually transmitted infections).

5. The protocol should include a list of prescription and over-the-counter drug products that are prohibited during the study, such as:
a. Any anticoagulation therapy.
b. Systemic corticosteroid or immunosuppressive drugs.
c. Systemic or topical antibiotics, other than study product.
d. Cimetidine.
e. Lithium.
f. Any product inserted into the vagina during treatment (e.g., on study Days 1-2) and for 48 hours prior to Test of Cure visit.
g. Subjects should be instructed not to engage in vaginal intercourse during treatment (e.g., on study Days 1-2). Subjects should be cautioned about drinking alcohol during treatment.

6. The primary endpoint of the study is the responder rate, defined as both a clinical cure [resolution of the abnormal vaginal discharge, a negative whiff (amine) test for any amine “fishy” odor (KOH Test), and the presence of clue cells at less than 20% of the total epithelial cells on microscopic examination of the saline wet mount]3, AND a bacteriological cure (Nugent score <4), evaluated at the Test of Cure visit (study Day 22-30).

7. Subjects who used any BV therapy, other than study product, during the study or had a Nugent score ≥4 at the Test of Cure visit should be considered therapeutic failures.

8. Please 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. 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

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3 Note that the inclusion criteria use all four Amsel criteria but only three are used to support the primary study endpoint.
v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
w. Baseline vaginal discharge consistent with clinical diagnosis bacterial vaginosis (yes/no)
x. Baseline clue cells on wet mount (≥20%, <20%, or none)
y. Baseline vaginal pH
z. Baseline KOH “whiff test” (positive/negative)
aa. Baseline Nugent score
bb. Chlamydia trachomatis (positive/negative)
cc. Neisseria gonorrhoeae test, (positive/negative)
dd. Urine pregnancy test (positive/negative)
ee. Clinical cure (Day 22-30) (yes/no)
ff. Normal physiological vaginal discharge (Day 22-30) (yes/no)
gg. KOH “whiff test” (Day 22-30) (positive/negative)
hh. Clue cells on wet mount (Day 22-30) (≥20%, <20%, or none)
ii. Bacteriological cure (Day 22-30) (yes/no)
jj. Nugent score (Day 22-30) (0, 1, 2, 3, or 4)
kk. Treatment success (Day 22-30) (responder) (yes/no)
ll. Compliance rate (%)
mm. Subject missed the pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
nn. Adverse event reported (yes/no)
oo. Concomitant medication (yes/no)

9. Please 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. Abnormal vaginal discharge (yes/no)
   o. Clinical cure (yes/no)
   p. Normal physiological vaginal discharge (yes/no)
   q. KOH “whiff test” (positive/negative)
   r. Clue cells on wet mount (≥20%, <20%, or none)
   s. Bacteriological cure (yes/no)
   t. Nugent score (0, 1, 2, 3, or 4)
u. Treatment success (responder) (yes/no)
v. Additional treatment required during the visit (yes/no)
w. Adverse event reported during the visit (yes/no)
x. Use of any vaginal products other than study product (yes/no)
y. Concomitant medication during the visit (yes/no)

10. Please refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled Guidance on Adapalene; Benzoyl Peroxide for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoint.

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

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4 Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber