

Contains Nonbinding Recommendations
Draft Guidance on Butoconazole Nitrate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Cream; vaginal

Recommended Studies: One study

1. Type of study: Bioequivalence with Clinical Endpoint Study
Design: Randomized, double blind, parallel, placebo-controlled in vivo
Strength: 2% [dose: one full applicator (5 g) of Butoconazole Nitrate Vaginal Cream, USP 2% (approximately 100 mg butoconazole nitrate) administered once]
Subjects: Postmenarcheal females with vulvovaginal candidiasis
Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): 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 guidance for industry *Controlled Correspondence Related to Generic Drug Development* and the guidance for industry *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 with clinical endpoint study:

1. The Office of Generic Drugs (OGD) recommends a clinical endpoint bioequivalence study comparing the Butoconazole Nitrate Vaginal Cream USP, 2% test product versus the reference product and placebo vehicle, each administered by inserting one full applicator (approximately 5 g) cream into the vagina once (Study Day 1), with the primary endpoint evaluation at the test-of-cure visit conducted on Study Day 21 to 30 (i.e., at the visit occurring between 20 to 29 days after administration of the last dose of vaginal cream).

2. Inclusion Criteria (the sponsor may add additional criteria):
 - a. Postmenarcheal female.
 - b. Clinical diagnosis of symptomatic vulvovaginal candidiasis (VVC) confirmed at baseline by positive KOH wet mount (i.e., when examined microscopically, vaginal secretions obtained by swab of the vaginal mucosa, placed on a slide and diluted with 10% room temperature potassium hydroxide (KOH) reveal filamentous hyphae/pseudohyphae and/or budding yeast cells).
 - c. Presence of at least one vulvovaginal sign (vulvovaginal erythema, edema, or excoriation) as assessed by the investigator at baseline.
 - d. Presence of at least one vulvovaginal symptom (vulvovaginal itching, burning, or irritation) as reported by the subject at baseline.
 - e. At baseline, $\geq 50\%$ of the subjects should have at least moderate severity of VVC, defined as having a minimum composite vulvovaginal signs and symptoms score of 7 (see Comment #8).
 - f. Documented Papanicolaou (Pap) test at baseline or during the previous 12 months reported as either “negative for intraepithelial lesion or malignancy” or “ASCUS-atypical squamous cells of undetermined significance”.

3. Exclusion Criteria (the sponsor may add additional criteria):
 - a. Pregnant or nursing.
 - b. Diabetes mellitus. [**NOTE:** If diabetic women are enrolled, it is important that their diabetes be controlled and the proportion of subjects with diabetes be similar among all treatment groups, because cure rates might differ in diabetic versus nondiabetic women.]
 - c. Use of systemic, topical (applied to the vulva) or vaginal antibiotics, antifungals or antitrichomonals within 7 days prior to randomization.
 - d. Use of any systemic corticosteroid, immunosuppressive, or immune-stimulating drug within 3 months prior to randomization.
 - e. Presence of concomitant vulvovaginitis caused by other infections (e.g., bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis* or *Neisseria gonorrhoeae*).
 - f. Presence of another vaginal or vulvar condition that would confound the interpretation of clinical response.
 - g. History of allergy or sensitivity to butoconazole nitrate, related compounds or any component of the formulation.

4. Vaginal discharge should not be an inclusion criterion or included in the evaluation of treatment as this sign cannot be consistently correlated with the presence or absence of VVC.

5. Positive vaginal fungal culture at baseline should not be an inclusion criterion due to the time lag between obtaining the culture specimen and receiving the culture results. However, a vaginal fungal culture must be obtained at baseline. Testing should be performed to identify the isolates to the species level (e.g., *Candida albicans*, *Candida tropicalis*, or *Candida glabrata*). Only subjects with a pretreatment, baseline vaginal fungal culture that is positive for a *Candida* species should be included in the per protocol (PP) and modified intent to treat (mITT) populations for the primary endpoint analysis.

6. Provide a listing of the prescription and over-the-counter drug products that are prohibited during the study, such as:
 - a. Topical products applied to the vulva or vagina (e.g., antibiotic, antifungal, antitrichomonal, corticosteroid or anti-inflammatory topical products).
 - b. Vaginal products other than study product (e.g., vaginal estrogen, vaginal progesterone, douches, spermicides, condoms, tampons, diaphragms, contraceptive cream, contraceptive foam, or contraceptive film).
 - c. Oral antibiotics, antifungals, or antitrichomonals.
 - d. Oral or injectable corticosteroid or immunosuppressive.

7. The recommended primary endpoint of the study is the proportion of subjects with therapeutic cure, defined as both mycological cure and clinical cure, at the test-of-cure visit conducted on study Days 21 to 30. Mycological cure is defined as a negative KOH wet mount test of vaginal secretions AND a negative vaginal fungal culture for *Candida* species. Clinical cure is defined as ALL of the following:
 - a. Any vulvovaginal sign or symptom with a baseline score of 1 or 2 (on a 4-point scale as provided in Comment #8) has a score of 0 (absent) at the test-of-cure visit on study Day 21 to 30.
 - b. Any vulvovaginal sign or symptom with a baseline score of 3 (on a 4-point scale as provided in Comment #8) has a score of 0 (absent) or 1 (mild) at the test-of-cure visit on study Day 21 to 30.
 - c. Any new sign or symptom observed at the test-of-cure visit is determined by the investigator not to be related to VVC.
 - d. The subject did not use any topical drug therapy (such as topical analgesics or corticosteroid products) other than the study product for the treatment of vulvovaginal irritation and/or pruritus.

8. Each of the following six vulvovaginal signs and symptoms should be individually scored using an accepted scale and then added together to determine the composite vulvovaginal signs and symptoms score.
 - a. **Vulvovaginal Signs:** erythema, edema, or excoriation
 - b. **Vulvovaginal Symptoms:** itching, burning, or irritation
 - c. **Scoring Scale:** Each score should be objectively defined. The following is an example of an acceptable scale.
 - 0 = none (absent)
 - 1 = mild (slight)
 - 2 = moderate (definitely present)
 - 3 = severe (marked, intense)

9. Subjects who receive or self-administer topical drug therapy for the treatment of vulvovaginal irritation/pruritus after the treatment phase of the study should be analyzed in the mITT and PP populations as a treatment failure.

10. Subjects with a negative vaginal fungal culture at baseline should be discontinued from the study and excluded from the PP and mITT populations but included in the safety population for the safety analyses.
11. 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.¹
12. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov²

¹ Product-Specific Guidances for Generic Drug Development available at:
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>

² Study Data Standards for Submission to CDER and CBER available at:
<https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm>