

Draft Guidance on Miconazole Nitrate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Miconazole Nitrate

Form/Route: Cream/Vaginal

Recommended studies: 1 study

Type of study: Bioequivalence (BE) with Clinical Endpoint Study

Design: Randomized, double blind, parallel, placebo-controlled in vivo

Strength: 2% [dose: one full applicator of miconazole nitrate 2% vaginal cream (100 mg miconazole nitrate) once daily at bedtime for 7 consecutive days]

Subjects: Healthy 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

Additional comments regarding the BE with clinical endpoint study:

1. The Office of Generic Drugs (OGD) recommends a clinical endpoint bioequivalence study comparing the miconazole nitrate 2% vaginal cream test product versus the reference listed drug (RLD) and placebo, each administered by inserting one full applicator of cream into the vagina once daily at bedtime for 7 consecutive days (study Day 1-7), with the primary endpoint evaluation at the test-of-cure visit conducted on study Day 21-30 (i.e., at the visit occurring between 14-23 days after administration of the last vaginal cream).
2. It is the sponsor's responsibility to enroll sufficient patients for the study to demonstrate bioequivalence between the products.
3. Assignment of the test product, RLD, and placebo should be randomized. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.
4. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in

treatment less obvious to the patients and to maintain adequate blinding of evaluators. When possible, neither the patient nor the investigator should be able to identify the treatment. The containers should not be opened by the patient at the study center.

5. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.
6. Inclusion Criteria (the sponsor may add additional criteria):
 - a. Healthy, 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 patient at baseline.
 - e. At baseline, $\geq 50\%$ of the patients should have at least moderate severity of VVC, defined as having a minimum composite vulvovaginal signs and symptoms score of 7 (see Comment #12).
 - 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”.
7. Exclusion Criteria (the sponsor may add additional criteria):
 - a. Pregnant or nursing. [**NOTE:** Pregnant women can be included in the study after completing the first trimester of pregnancy. If pregnant women are enrolled, it is important that the proportion of pregnant patients be similar among all treatment groups, because cure rates might differ in pregnant versus nonpregnant women.]
 - b. Diabetes mellitus. [**NOTE:** If diabetic women are enrolled, it is important that their diabetes be controlled and the proportion of diabetic patients 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. Use of anticoagulation therapy (e.g., warfarin).
 - f. Presence of concomitant vulvovaginitis caused by other infections (e.g., bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis* or *Neisseria gonorrhoeae*).
 - g. Presence of another vaginal or vulvar condition that would confound the interpretation of clinical response.
 - h. History of allergy or sensitivity to miconazole nitrate, related compounds or any component of the formulation.

8. 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.
9. 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 patients 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.
10. Provide a listing of the prescription and over-the-counter drug products that are contraindicated 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.
 - e. Anticoagulation therapy (e.g., warfarin)
11. The recommended primary endpoint of the study is the proportion of patients with therapeutic cure, defined as both mycological cure and clinical cure, at the test-of-cure visit conducted on study Days 21-30. 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 #11) has a score of 0 (absent) at the test-of-cure visit on study Day 21-30.
 - b. Any vulvovaginal sign or symptom with a baseline score of 3 (on a 4-point scale as provided in Comment #11) has a score of 0 (absent) or 1 (mild) at the test-of-cure visit on study Day 21-30.
 - 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.
12. 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)

13. To establish bioequivalence, the 90% confidence interval of the difference in therapeutic cure rates between the test product and RLD treatment groups at the test-of-cure visit (study Day 21-30) must be within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP study population.
14. As a parameter for establishing study sensitivity, the test product and RLD should both be statistically superior to placebo ($p < 0.05$) with regard to the therapeutic cure rate at the test-of-cure visit (study Day 21-30), using the mITT study population and Last Observation Carried Forward (LOCF).
15. The sponsor should clearly define the PP, mITT and safety patient populations in the protocol.
16. The accepted PP population used for bioequivalence evaluation includes all randomized patients who had a positive baseline vaginal fungal culture for *Candida* species, were compliant with the assigned study product, and completed the evaluation at the test-of-cure visit within the designated visit window (study Day 21-30) with no protocol violations that would affect the treatment evaluation. The protocol should provide a definition of compliant patients (e.g., having used at least 75% and no more than 125% of study drug doses) and specify how compliance will be verified, e.g., by the use of patient diaries.
17. The usual mITT population includes all randomized patients who had a positive baseline vaginal fungal culture for *Candida* species, used at least one dose of study product, and returned for at least one post-baseline visit.
18. The usual safety population includes all randomized patients who received study product.
19. Patients who are discontinued early from the study due to lack of treatment effect after completing 6 consecutive days of treatment should be included in the PP population as treatment failures (i.e., non-responders). Patients discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF.
20. Patients 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.
21. Patients 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.
22. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.
23. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.

24. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment should be contained within [-0.20, +0.20] in order to establish equivalence.

The compound hypothesis to be tested is:

$$H_0: p_T - p_R < -0.20 \text{ or } p_T - p_R > 0.20$$

versus

$$H_A: -0.20 \leq p_T - p_R \leq 0.20$$

where p_T = cure rate of test treatment p_R = cure rate of reference treatment.

Let

n_T = sample size of test treatment group

$c n_T$ = number of cured patients in test treatment group

n_R = sample size of reference treatment group

$c n_R$ = number of cured patients in reference treatment group

$$\hat{p}_T = c n_T / n_T, \quad \hat{p}_R = c n_R / n_R,$$

$$\text{and se} = \left(\hat{p}_T (1 - \hat{p}_T) / n_T + \hat{p}_R (1 - \hat{p}_R) / n_R \right)^{1/2}.$$

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = \left(\hat{p}_T - \hat{p}_R \right) - 1.645 \text{ se} - (1/n_T + 1/n_R)/2$$

$$U = \left(\hat{p}_T - \hat{p}_R \right) + 1.645 \text{ se} + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

25. Study data should be submitted to the OGD in electronic format.
- a. A list of file names included in the CD or diskette(s), with a simple description of the content of each file, should be included.

- b. Please provide a “pdf” document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
 - c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
 - d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
 - e. Please provide a separate dataset for variables as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.
26. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
- a. Study identifier
 - b. Subject identifier
 - c. Site identifier: study center
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of Actual Treatment (exposure): test product, RLD, placebo
 - i. Duration of Treatment (total exposure in days)
 - j. Per Protocol (PP) population inclusion (yes/no)
 - k. Reason for exclusion from PP population
 - l. Modified Intent to Treat (mITT) population inclusion (yes/no)
 - m. Reason for exclusion from mITT population
 - n. Safety population inclusion (yes/no)
 - o. Reason for exclusion from safety population
 - p. Final designation as therapeutic cure (yes/no)
 - q. Treatment compliance: number of missed doses per patient
 - r. Concomitant medication (yes/no)
 - s. Adverse event(s) reported (yes/no)

Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXDUR	pp	pp_rs	mitt	mitt_rs	safety	safe_rs	cure	complan	CM	AE
101	1	01	22	YEARS	F	1	A	3	Y		Y		Y		N	0	Y	Y
101	2	01	30	YEARS	F	1	B	3	Y		Y		Y		Y	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Draft dated 7/25/07.

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., F, U for Female, Unknown
RACE:	Race, e.g. 1, 2, 3, 4, 5 (1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders)
EXTRT:	Name of Actual Treatment (exposure), e.g. A=test product, B= RLD, C=placebo
EXDUR:	Duration of Treatment (total exposure in days)
pp:	Per Protocol (PP) population inclusion, e.g., Y, N (Yes or No)
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt:	Modified Intent to Treat (mITT) population inclusion, e.g., Y, N (Yes or No)
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety:	Safety population inclusion, e.g., Y, N (Yes or No)
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
cure:	Final designation (i.e., Yes=therapeutic cure, No=failure)
complan:	Treatment compliance, e.g., number of missed doses per patient
CM:	Concomitant medication, e.g., Y, N (Yes or No)
AE:	Adverse event(s) reported, e.g., Y, N (Yes or No)

27. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:

- a. Study identifier
- b. Subject identifier
- c. Name of Actual Treatment (exposure): test product, RLD, placebo control
- d. Visit number
- e. Visit date
- f. Number of days since baseline visit
- g. Evaluator: identity of evaluator
- h. Vulvovaginal erythema score
- i. Vulvovaginal edema score
- j. Vulvovaginal excoriation score
- k. Vulvovaginal itching score
- l. Vulvovaginal burning score
- m. Vulvovaginal irritation score
- n. Composite vulvovaginal signs and symptoms score
- o. KOH result
- p. Culture result
- q. Mycological cure (yes/no)
- r. Clinical cure (yes/no)
- s. Therapeutic cure (yes/no)
- t. Concomitant medication reported during this visit (yes/no)
- u. Adverse event reported during this visit (yes/no)
- v. Laboratory testing during this visit (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	EVAL	erythema	edema	excoriat	itching	burning	irritat	compvv	koh	culture	mycocure	clincure	thercure	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	18	JB	0	0	1	1	0	0	1	Pos	Pos	N	N	N	Y	Y	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Draft dated 7/25/07.

- STUDYID: Study Identifier
- SUBJID: Subject Identifier for the Study
- EXTRT: Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C= placebo control
- VISITNUM: Visit Sequence Number
- SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
- ELTMBS: Elapsed Time since Baseline (days)
- EVAL: Evaluator: identity of the evaluator (e.g., initials)
- erythema: Vulvovaginal erythema score, e.g. 0=none (absent), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
- edema: Vulvovaginal edema score, e.g. 0=none (absent), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
- excoriat: Vulvovaginal excoriation score, e.g. 0=none (absent), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
- itching: Vulvovaginal itching score, e.g. 0=none (absent), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
- burning: Vulvovaginal burning score, e.g. 0=none (absent), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
- irritat: Vulvovaginal irritation score, e.g. 0=none (absent), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
- compvv: Composite vulvovaginal signs and symptoms score
- koh: KOH, e.g., Pos, Neg (Positive or Negative)
- culture: Culture, e.g., Pos, Neg (Positive or Negative for Candida species)
- mycocure: Mycological cure, e.g., Y, N (Yes or No)
- clincure: Clinical cure, e.g., Y, N (Yes or No)
- thercure: Therapeutic cure, e.g., Y, N (Yes or No)
- CMrpt: Concomitant Medication reported during this visit, e.g., Y, N (Yes or No)
- AErpt: Adverse Event reported during this visit, e.g., Y, N (Yes or No)
- LBtest: Laboratory Testing performed during this visit, e.g., Y, N (Yes or No)

28. Sponsors may submit a protocol for review and comment prior to conducting the study.