

Guidance for Industry

Vulvovaginal Candidiasis — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573, or from the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

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GUIDANCE FOR INDUSTRY¹

Vulvovaginal Candidiasis — Developing Antimicrobials for Treatment

I. INTRODUCTION

This is one in a series of guidance documents intended to assist the pharmaceutical industry in the development of antimicrobial drug products for the treatment of infections. The information presented here should help applicants plan clinical studies, design clinical protocol(s), implement and appropriately monitor the conduct of clinical studies, collect relevant data for analysis, and perform appropriate types and numbers of analyses of study data. Clinical trials planned and conducted as recommended in this guidance should yield the information necessary for the Agency to determine whether the antimicrobial under study is safe and effective in the treatment of the specific infection. For general information on related topics, the reader is referred to the guidance *Developing Antimicrobial Drugs — General Considerations for Clinical Trials (General Considerations)*.

This guidance for industry focuses on developing antimicrobials for the treatment of vulvovaginal candidiasis (VVC). The guidance presents information related to VVC prescription products only. Clinical trial design guidance for the over-the-counter (OTC) treatment of VVC will be developed subsequently in collaboration with CDER's Division of Over-the-Counter Drug Products.

II. BACKGROUND

Over the years, the Agency has issued guidance to the pharmaceutical industry on how to design, carry out, and analyze the results of clinical trials for the development of antimicrobials for the

¹ This guidance has been prepared by the Office of Drug Evaluation IV, representing the Division of Anti-Infective Drug Products, the Division of Special Pathogens and Immunological Drug Products, and the Division of Anti-Viral Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on developing antimicrobials for the treatment of vulvovaginal candidiasis. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

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treatment of infections in a variety of forms. Guidance has been provided verbally during various industry and FDA meetings, in letters written to sponsors, and in general guidance on related issues. This guidance is the result of efforts to collect all pertinent information and present it in one location. Where appropriate, this guidance contains relevant information from several sources, including *Clinical Evaluation of Anti-Infective Drugs (Systemic)* (1977); IDSA's "Guidelines for the Evaluation of Anti-Infective Drug Products" (1992) (IDSA guidance);² *Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products* (1992) (*Points to Consider*), an FDA guidance on issues related to evaluating new drug applications for anti-infective drug products; and *Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products* (February 1997), a draft guidance discussed at a March 1997 advisory committee meeting on anti-infective drug products, which will be superseded by this guidance once it is issued in final form.

The regulatory history and background of drug development for the treatment of VVC is noteworthy. Until 1990, all topical vaginal antifungal drug products that were approved by the U.S. Food and Drug Administration (FDA) for the treatment of vulvovaginal candidiasis were available by prescription only. In 1990, the FDA convened an advisory committee meeting to obtain expert opinions whether treatments for vulvovaginal candidiasis should be made available for OTC use. By unanimous vote, the advisory committee recommended that women who had previously been diagnosed by a physician as having VVC and then developed the same symptoms as they had when the diagnosis was made can adequately self-treat their disease with an approved 7-day OTC product. Currently several products in the azole class of antifungal agents (clotrimazole, miconazole, butoconazole, and tioconazole) are approved as OTC products for treating VVC.

III. VULVOVAGINAL CANDIDIASIS

A. Regulatory Synonyms

A number of synonyms have been used in the past in discussions of VVC, including *candidal vaginitis*, *vaginal candidiasis*, *vaginitis due to *Candida albicans**, *moniliasis*, *yeast vaginitis*, or *vulvovaginal candidiasis*.

B. Study Considerations

Two statistically adequate and well-controlled multicenter trials should be conducted establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). Because

² This guidance appeared in IDSA's (Infectious Disease Society of America) supplement to *Clinical Infectious Diseases*, formerly *Reviews of Infectious Diseases*.

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this infection is not related to other vaginal infections and interpretation of microbiological results is problematic, a 7-day comparative regimen is recommended as the control agent to ensure that biocreep (where treatment regimens of shorter duration may be less effective than 7-day products) does not go unrecognized as dosing regimens are progressively shortened.

In addition, corroborative evidence can best be obtained from a second adequate and well controlled clinical trial (because this infection is not related to other vaginal infections and validated surrogate endpoints are unknown).

1. Randomization

Patients should be randomized to a study arm after a screening, positive KOH test result is obtained.

2. Blinding

These studies should be investigator-blinded and conducted without the use of a vehicle (the drug product minus the active ingredient). There is concern that the use of either intravaginal or topical, external vulvar placebos may alter clinical outcomes in many ways (e.g., cause local relief when applied to inflamed mucosa or epithelium, dilute or displace the active drug product from the site of infection). The plan for investigator blinding should be described in the protocol.

3. Patient Follow-up

All patients randomized should be followed throughout the study period, even if there are deviations from the protocol. In other words, study withdrawals should be minimized.

C. Inclusion Criteria

Postmenarchal females with a diagnosis of VVC should be included based on the criteria listed below.

To be clinically evaluable, patients should have a clinical diagnosis of VVC based on history and physical examination (including vaginal exam). Signs and symptoms to be evaluated include: itching, burning, irritation, edema, erythema and/or excoriation of the vagina/vulva. Each evaluated sign and/or symptom should be given a numerical rating based on severity (absent = 0; mild = 1; moderate = 2; severe = 3).

The patient should have a minimum composite signs/symptoms score equal to 2. It is recommended that 50% or more of the evaluable patients should have clinical evidence of disease

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of at least moderate severity at entry, defined as having a minimal composite score of 7. Severe disease is defined as a minimal composite sign/symptom score of 13.

Patients with VVC may have a vaginal discharge, which is usually described as white, creamy, and curdy (cottage cheese-like) in appearance and adherent to the epithelium. The presence or absence of this discharge, however, should not be rated as a clinical sign or symptom of infection in considering a patient clinically evaluable.

A Papincolaou (Pap) test should be obtained at study entry or a Pap test result from the previous 12 months should be entered onto the case report form.

A screening KOH preparation from the inflamed vaginal mucosa should reveal yeast forms (hyphae/pseudohyphae) or budding yeasts and an entry culture should be positive for *Candida albicans* or one of the other *Candida* species. Testing should be performed to identify the isolates to the species level (e.g., *Candida albicans*, *Candida tropicalis*, *Candida glabrata*). In-vitro susceptibility testing using standardized methods should be performed to determine minimum inhibitory concentrations (MICs). Antifungal drug products under study are expected to exhibit acceptable in vitro activity against the causative *Candida* spp. isolated from the patients enrolled in clinical trials.

The majority of the cases of VVC are caused by the yeast *Candida albicans*. However, in some published series, it is reported that as many as 20-30% of VVC cases are due to other fungal species, such as *Candida tropicalis* and *Candida glabrata* (formerly *Torulopsis glabrata*). These species may be more resistant to OTC antifungal agents. The antifungal activity of a therapeutic agent/regimen can be characterized best by obtaining additional microbiologic information (i.e., identification of fungal species and drug resistance patterns) collected during clinical trials. Therefore, it is recommended that in all phase 2 and 3 clinical trials, fungal isolates recovered from patients at entry and at follow-up visits should be identified to the species level, as well as tested in vitro to determine the susceptibility of fungal isolates to the antifungal agent/regimen.

D. Exclusion Criteria

Patients should be excluded on the basis of the following criteria:

- Patients who received intravaginal or systemic antifungal therapy within 7 days of randomization
- Patients with other infectious causes of vulvovaginitis (e.g., bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Herpes simplex*, or human papilloma virus)

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- Patients with another vaginal or vulvar condition that would confound the interpretation of clinical response
- Women who will be under treatment or surgery during the study period for cervical intraepithelial neoplasia (CIN) or cervical carcinoma
- Patients who are pregnant, unless the drug has been shown to be safe for use in pregnancy or a risk/benefit justification is provided in the protocol and brought to the attention of the reviewing division

E. Drugs and Dosing Regimen

Patients should be provided with a diary at the time that drug is dispensed (see Attachment). Each patient should accurately document in her diary the date and time when each dose is administered. If any doses are missed, the reason(s) for noncompliance should be entered in the diary.

Lot numbers and other identifiers should be provided for all study drugs.

Evaluability depends on the proposed treatment duration for the study arm and the number or proportion of the doses taken, as summarized below:

- *One day:* 1 dose is considered evaluable
- *Three days:* 3 doses are considered evaluable
- *Seven days:* 3 doses (3 consecutive days) are considered evaluable

F. Evaluation

Until recently, it was recommended that patients attend three clinic visits during the course of a study. The current recommendation is that two study visits, a patient diary, and an interim telephone contact are sufficient to adequately characterize the safety and efficacy of a drug product intended to treat VVC. These visits include the entry visit and the test-of-cure visit at 21 to 30 days of the study. Windows of evaluability are designed to accommodate for holidays, weekends, and menses.

1. Entry Visit

At entry, the patient should be questioned about her past medical history and the present infection, the patient should have a physical examination performed including speculum

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examination of the vagina, KOH preparation should be evaluated, a vaginal specimen obtained for culture and susceptibility testing results and samples should be collected for baseline chemistry, hematology and urinalysis tests. All the results from these procedures should be documented in the case report form.

The number of episodes of VVC diagnosed and the treatment given in the preceding 12 months should be documented on the case report form.

A wet prep should be done to rule out infection due to *Trichomonas vaginalis* and to rule out clue cells associated with bacterial vaginosis. Specimens should be sent for culture to rule out *Chlamydia tracomatis* and *Neisseria gonorrhoeae*. If *Herpes simplex* virus is suspected, viral cultures should be done. Pap smear should be performed to rule out human papilloma virus.

Patients should begin using the study drug within 2 days of the entry visit to be considered evaluable.

Patients should be encouraged to refrain from the use of intravaginal products during the treatment period (e.g., douches, spermicides, condoms, tampons, diaphragms) because use of such products may preclude accurate assessment of the study drug's efficacy as well as safety.

In the consent form and before leaving the study facility, the patient should be told that if her symptoms don't improve within 2 to 3 days, she should contact the investigator and be reassessed at an office visit. Similarly, if other adverse events occur that concern the patient, she should be encouraged to contact the investigator.

2. Post-Treatment Telephone Contact

This post-therapy contact should be initiated by the investigator and occur approximately 7 to 10 days after the beginning of therapy. The purpose of this visit is to ensure patient compliance with the protocol and to evaluate the patient's response to therapy, as well as to inquire about possible adverse events. The patient should be reminded to properly record data in her diary. As above, if during the telephone interview the patient's clinical response is considered inadequate, the investigator should ask the patient to come to the treatment center for a full evaluation. If the patient can't be contacted by telephone, she may be considered evaluable (as long as all other evaluability criteria are fulfilled).

3. Test-of-Cure Visit

This visit should occur 21 to 30 days after the first day of treatment. At this visit, clinical

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history, vaginal examination, and a vaginal semi-quantitative culture should be repeated. Speciation and susceptibility testing should be done on all positive cultures. Quantification as to the amount of fungal growth on culture should be recorded as 1+ to 4+.

The same signs and symptoms as evaluated at the entry visit should be reassessed: itching, burning, irritation, edema, erythema and/or excoriation of the vagina and/or the vulva.

Each evaluated sign and/or symptom should be given a numerical rating based on severity (absent = 0; mild = 1; moderate = 2; severe = 3).

The investigator should answer the following question on the case report form:

In your opinion, does the patient require additional treatment for vulvovaginal candidiasis at this time? (yes/no) If yes, please explain why. _____

G. Outcome

1. Clinical Outcome

The patient should have signs and symptoms of vulvovaginal candidiasis at the entry visit, should meet the inclusion and exclusion criteria, should be compliant with the study regimen, and should return for the post treatment visit at study days 21 to 30. The patient should have received no additional vulvovaginal or systemic antifungal drug during the study period covering days 1 to 30, other than allowed per protocol.

If a patient uses other vaginal products (e.g., douche, N-9 products, condoms, tampons) during the treatment phase of the study (e.g., days 1 to 7), she will be considered nonevaluable. Patients who use these vaginal products after completing treatment (e.g., days 8 to 30) should be analyzed as a separate subset and then combined with the per protocol evaluable population.

- *Clinical Cure:* Resolution of signs and symptoms of vulvovaginal infection during treatment and by the time of the 20- to 30-day test-of-cure visit and without further antifungal treatment. Specifically, any sign or symptom with a score of 1 or 2 at entry should be absent (score = 0) by the test-of-cure visit. Any sign or symptom with a score of 3 (severe) at entry should have a score of 0 or 1 by the test-of-cure visit. If a new sign or symptom is observed at the test-of-cure visit

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that was not present at entry, the investigator should state whether the new sign or symptom is related to VVC or not (i.e., if related, the patient would be considered a failure; if not related, she may be considered a cure).

- *Clinical Failure:* No response to therapy or incomplete resolution of signs and symptoms or need for additional vulvovaginal or systemic antifungal therapy. If the patient receives or self-administers topical drug therapy for the treatment of vulvovaginal irritation/pruritus such as topical analgesic or corticosteroid after completing treatment with the study drug and before the test-of-cure visit, the patient is considered a clinical failure.

In answering the question, “In your opinion, does the patient require additional treatment for vulvovaginal candidiasis at this time,” if the investigator answers “yes” to this question, then the patient should be considered a clinical failure.

2. Mycological Outcome

In addition to meeting the definition of clinically evaluable, the patient should have a positive KOH at entry and should have *Candida albicans* (or another *Candida* species) isolated from a culture of the vaginal specimen.

- *Mycological Eradication:* A patient with negative culture (no growth) for *Candida albicans* (or baseline yeast pathogen) at the test-of-cure visit, days 21 to 30 of the study.
- *Mycological Persistence:* A patient with a positive culture for *Candida albicans* (or baseline yeast pathogen) at the test-of-cure visit, days 21 to 30 of the study.

3. Therapeutic Outcome

The overall therapeutic assessment is derived by taking into consideration both the clinical and mycological responses. (See table below.)

- *Therapeutic Cure:* Patient who is considered both clinical cure and mycological eradication at V2.
- *Therapeutic Failure:* Patient who at sometime during the study period (days 3 to 30) was considered by the investigator as either a clinical failure or mycological persistence. (See above.)

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DETERMINATION OF THERAPEUTIC RESPONSE BY THE TEST-OF-CURE VISIT AT STUDY DAYS 21-30 (SUMMARIZED)		
If the clinical outcome is...	and the mycological outcome is...	then the overall therapeutic outcome is...
cure	no growth	cure
cure	growth	failure
failure	no growth	failure
failure	growth	failure
failure	missing or not interpretable	failure
cure	missing or not interpretable	non-evaluable
non-evaluable	no growth	non-evaluable
non-evaluable	growth	failure

4. Safety Outcome

In general, when topically applied antifungals show minimal systemic absorption (based on pharmacokinetic studies), safety assessments can be limited to local descriptions of toxicity. However, where appreciable systemic absorption occurs, hematology, chemistry, and urine laboratory testing should be performed at both entry and test of cure visits to assess organ toxicity.

H. Statistical Considerations

1. Analytical Considerations

Two analyses should be performed: The subset of the enrolled population should be analyzed that qualifies for the assessment of therapeutic outcome by being considered both clinically evaluable and mycologically evaluable. This is also referred to as the per protocol analysis or the primary analysis. As defined in the table above, if either the clinical or the mycological outcome is missing, then the assumption is that this outcome should be considered a failure or persistence, respectively.

Intent-to-treat analysis should be performed, which includes all women randomized into the study. In this case, patients who have missing outcome data would be considered to have the worst-case-scenario outcome and be classified as a clinical failure/mycological persistence.

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2. Evaluations

The primary efficacy variable is considered the therapeutic cure rate. Because this is a composite endpoint, made up of the clinical cure rate and the mycological eradication rate of individual fungal species, the latter should be analyzed as secondary efficacy variables.

Based on the daily record in the patient diary, a time-to-resolution analysis should be performed.

Other analyses should include:

- Cross-tabulation of clinical cure and mycological eradication
- Summary of disease severity at baseline

3. Sample Size

Each study should be adequately powered to demonstrate therapeutic equivalence (using a 95% confidence interval around the difference in therapeutic cure rates) of the test drug to the comparator for the per protocol evaluable population.

There should also be a minimal number of patients exposed to the investigational product (same formulation and duration of therapy) during all phases of clinical testing to provide for adequate evaluation of the safety of the drug.

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ATTACHMENT

Recommended Patient Diary

We would like to know if the medicine you have been given relieves the discomfort you have been feeling. Please let us know by answering the questions below. Check the box that you feel best describes your symptoms after using the medication.

SYMPTOM RELIEF CARD						
After Using the Medication My Symptoms were	Completely gone	Much better	A little better	No change	A little worse	Much worse
30 minutes after the first dose						
Prior to the 2 nd bedtime dose						
Prior to the 3 rd bedtime dose						
Prior to the 4 th bedtime dose						
Prior to the 5 th bedtime dose						
Prior to the 6 th bedtime dose						
Prior to the 7 th bedtime dose						

If your symptoms weren't completely gone until after day 7, please indicate on which date _____.

If your symptoms returned, please indicate on which date _____.

Please Record the date you took each dose of Study Medicine below:

1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ 7. _____

Please circle one or more of the following products, if you used them during the first 7 days after starting the drug:

spermicide tampon douche condom diaphragm

Please circle one or more of the following products, if you used them between day 7 of the study and the return clinic visit:

spermicide tampon douche condom diaphragm