

Draft Guidance on Clotrimazole

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Clotrimazole

Form/Route: Troche/Lozenge; Oral

Recommended studies: 1 study

Type of study: Clinical Endpoint Bioequivalence Study

Design: An *in vivo* randomized, blinded, parallel design bioequivalence study with clinical endpoints.

Strength: 10 mg

Subjects: Patients with oropharyngeal candidiasis.

Additional comments:

1. Patients who meet inclusion/exclusion criteria are to be randomly assigned to treatment with the test or reference product for 14 days, and the primary endpoint for bioequivalence is clinical cure 7 days after the end of therapy (Day 21) in the evaluable per protocol population.
2. The recommended dose is one troche five times a day (at approximately 3-4 hour intervals) for fourteen consecutive days. Each troche is to be slowly dissolved in the mouth.
3. A placebo arm is not recommended for this study because the affected population is mostly immunocompromised and tends to have relatively advanced disease such that deferring therapy by giving placebo is not considered to be safe or ethical.
4. The accepted primary endpoint of this study is the proportion of patients in the per protocol analysis population with clinical cure, defined as complete resolution of all signs and symptoms of oropharyngeal candidiasis.
5. Presence or absence of specific signs and symptoms of oropharyngeal candidiasis, including erythematous areas, white patches, mouth pain, altered taste, pruritus, dysphagia, and/or odynophagia, should be recorded at each visit.
6. At Day 8 patients are to be evaluated for a clinical response defined as improvement in both symptoms of oropharyngeal candidiasis and examination of the oropharynx. If the patient has not improved, he/she is to be discontinued from the study, analyzed as a treatment failure, and provided with effective therapy.
7. At Day 15 clinical and mycological evaluation are to be performed. Regardless of culture and KOH microscopic evaluations at this visit, all patients showing clinical improvement are

to be continued in the study without further treatment and evaluated for clinical cure at the Day 21 visit. Any patient with worsening symptoms prior to Day 21 is to be discontinued from the study, analyzed as a treatment failure, and provided with effective therapy.

8. Culture results at Day 15 are to be evaluated for mycological cure as a secondary endpoint. Clinical cure at Day 15 may also be evaluated as a secondary endpoint. Culture results at Day 21 may be evaluated as an additional secondary endpoint. The recommended visit window is within ± 4 days of the designated endpoint visit day to be considered evaluable.
9. Reduction in symptoms is not considered an acceptable endpoint. Complete resolution of all signs and symptoms is required for a clinical cure. Mycological improvement is not considered an acceptable endpoint. Mycological cure (negative culture and negative KOH) at the end of treatment is recommended as a secondary endpoint.
10. Recommended Inclusion Criteria (the sponsor may add additional criteria):
 - a. Presence of specific signs and symptoms of oropharyngeal candidiasis, including erythematous areas, white patches, mouth pain, irritation, burning, glossitis, altered taste, and/or pruritus
 - b. Clinical examination of oropharynx consistent with a diagnosis of oral candidiasis (such as creamy, white, curd-like patches of “thrush” or erythematous lesions on mucosal surfaces)
 - c. Findings on direct microscopic examination (potassium hydroxide smear) consistent with *Candida* species or positive fungal culture for *Candida* species, with culture obtained in the 2 days preceding initiation of therapy with the study drug.
11. Recommended Exclusion Criteria (the sponsor may add additional criteria):
 - a. CD4 cell count less than 200 cells/mm³
 - b. Absolute neutrophil count less than 500/mm³
 - c. Pregnant or breastfeeding or planning to become pregnant during the 21-day study period.
 - d. Diagnosed with disseminated candidiasis or requires systemic antifungal therapy.
 - e. Diagnosed with hairy leukoplakia.
 - f. Presence of only perioral lesions, e.g., angular cheilitis
 - g. Exhibits signs or symptoms of candidal esophagitis (i.e., odynophagia or dysphagia) unless the results of an endoscopic evaluation of the esophagus are negative.
 - h. History of intolerance (e.g., elevation of liver enzymes) or sensitivity to clotrimazole (or other imidazole or azole compounds) or any constituent of Mycelex® or the generic product, or unable to tolerate oral medication.
 - i. History of resistance to treatment with clotrimazole.
 - j. Has received any oral or systemic antifungal therapy within fourteen (14) days prior to randomization.
 - k. Has received any investigational therapy within 30 days prior to randomization.
 - l. Diagnosed with any concomitant condition that, in the opinion of the investigator, could interfere with the evaluation of efficacy or safety, or would make it unlikely that the subject would complete the study.
 - m. Has been treated with protease inhibitors for the first time within 30 days
 - n. Has been taking medications known to have significant interaction with azoles (e.g., antacids, H₂-receptor blockers, rifampin, phenytoin, carbamazepine, astemizole).

- o. Has a history of candidal prophylaxis with any azole antifungal medication.
 - p. Any patient with recurrent oropharyngeal candidiasis.
 - q. Any patient who is chronically infected with *Candida*.
 - r. Any patient with baseline liver function tests > 3 x the upper limit of normal (ULN).
12. Patients receiving topical antifungal therapy to a different area of the body need not be discontinued. However, the treatment site should be specified to allow the reviewer to confirm that those patients are evaluable. Patients requiring systemic antifungal therapy for reasons unrelated to the oral candidiasis should be discontinued and excluded from the PP population. Patients requiring systemic antifungal therapy for oral candidiasis are to be discontinued and analyzed as treatment failures.
13. It is the sponsor's responsibility to adequately power the study in order to demonstrate bioequivalence. The sample size calculation should be based on the primary endpoint of the study and the expected treatment response for the reference product.
14. The following Statistical Analysis Method is recommended:

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within (-.20, +.20) in order to establish equivalence.

The compound hypothesis to be tested is:

$$H_0: p_T - p_R < -.20 \text{ or } p_T - p_R > .20$$

versus

$$H_A : -.20 \leq p_T - p_R \leq .20$$

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

Let

n_T = sample size of test treatment group

cn_T = number of cured patients in test treatment group

n_R = sample size of reference treatment group

cn_R = number of cured patients in reference treatment group

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

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

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

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

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

We reject H_0 if $L \geq -.20$ and $U \leq .20$

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

15. In order to maintain blinding and to minimize bias, the randomization code is to be generated by an independent third party, or by the sponsor only if not involved in packaging and labeling of study medication.
16. A sealed copy of the randomization scheme is to be retained at the study site and should be available to FDA investigators at the time of site inspection to allow verification of the treatment identity for each patient.
17. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of both the test and reference 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.
18. You should clearly define the per protocol (PP) population. This should consist of all randomized patients who met all inclusion/exclusion criteria, complied with the minimum treatment course, returned to the study site for the primary endpoint visit within the specified window (+/- 4 days) OR discontinued from the study as a treatment failure, and did not have any protocol violations.
19. You should clearly define the intent-to-treat (ITT) patient population. This population should include those patients who meet all inclusion and exclusion criteria, have received study medication and who have returned for at least one post baseline visit. The ITT population is usually used to compare both test and reference products to placebo. However, a placebo arm is not recommended for this bioequivalence study, and the ITT population provides only supportive information.
20. The safety population should include all patients that receive study medication.
21. Patient compliance should be clearly defined *a priori* (e.g., compliant patients may be defined as having taken at least 75% and no more than 125% of doses). It is also recommended that patient compliance be evaluated by using patient diaries.

22. All patients who discontinue because of lack of treatment effect should be analyzed in the ITT and Per Protocol populations as a treatment failure and should be provided with effective alternate therapy. Patients who discontinue for reasons unrelated to treatment effect should be analyzed in the ITT population with last observation carried forward (LOCF) and should be excluded from the PP population.

23. For clinical endpoint bioequivalence studies of locally acting drug products, it is important that all treatment related adverse events be recorded to allow a comparison between generic and reference products and to ensure that the generic is no worse than the RLD with regard to these expected AEs, as well as unexpected AEs. You must include a provision in your protocol to compare the test and reference product with regard to the occurrence and severity of drug-related AEs. The safety analyses should include all patients who received a dose of study medication.

24. 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 you use for each variable in each of the SAS datasets (for example, 0=yes, 1=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). For each patient, the following variables should be contained in the data set:
 - Center/site, patient/subject number
 - Sex, race, age
 - Drug/treatment,
 - Safety population (yes/no), reason for exclusion from safety population
 - ITT population (yes/no), reason for exclusion from the ITT population
 - PP population (yes/no), reason for exclusion from the PP population
 - Final outcome (clinical cure vs. failure)

For each visit, including baseline visit if data exist per each patient, the following variables should be contained in the data sets:

- Visit number, date of visit, visit days from baseline
- Reason for exclusion from ITT per visit
- Reason for exclusion from PP per visit
- Presence or absence of each sign/symptom
 - Erythematous areas
 - White patches

Mouth pain
Altered taste
Pruritis
Dysphagia
Odynophagia
Mycological culture result/KOH evaluation
Clinical exam findings
Laboratory results
Adverse events
Reason for discontinuation

- e. Secondary data sets: SAS transport files should cover all variables collected in the Case Report Form (CRF) per patient. You should provide a single file for each field such as demographics, baseline admission criteria and vital variables, clinical variables for each visit plus visit date, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.
25. Please refer to 21 CFR 320.38 and 320.63 regarding retention of study drug samples. For more information, please refer to the Guidance for Industry: “Handling and Retention of BA and BE Testing Samples” (May 2004). Retention samples should be randomly selected from each drug shipment by each study site and retained by the investigator or an independent third party not involved with packaging and labeling of the study products. Retention samples should not be returned to the sponsor at any time. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline.”
26. These recommendations are specific to this product and may not be appropriate for BE studies of any other product, including any other dosage form or strength of clotrimazole.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.fda.gov/cder/ogd/index.htm>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.