

Draft Guidance on Miconazole

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablet/Buccal

Recommended studies: 1 study

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

Design: Randomized, double blind, parallel, in vivo

Strength: 50 mg

Subjects: Males and nonpregnant females with oropharyngeal candidiasis and documented HIV seropositivity

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: Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. 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.

Additional comments regarding the BE study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with a clinical endpoint in treatment of oropharyngeal candidiasis (OPC). Subjects are to be randomized to receive the generic miconazole buccal 50 mg tablet (test product) or the reference listed drug (RLD) 50 mg tablet placed on the gum region once daily in the morning, after brushing the teeth for 14 consecutive days. The tablet should be applied with dry hands. The tablet should be placed against the upper gum just above the incisor tooth (canine fossa) and held in place with slight pressure over the upper lip for 30 seconds to ensure adhesion. Subsequent application of the tablet should be made to alternate sides of the mouth. Before applying the next tablet, the subject should clear away any remaining tablet material.

As described in the approved labeling of the RLD, the tablet should not be crushed, chewed, or swallowed. If the tablet does not adhere or falls off within the first 6 hours, the same tablet should be repositioned immediately. If the tablet still does not adhere, a new tablet should be placed. If the tablet is swallowed within the first 6 hours, the subject should drink a glass of

water and a new tablet should be applied only once. If the tablet falls off after it was placed for 6 hours or more, a new tablet should not be applied until the next regularly scheduled dose.

2. A placebo control 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.
3. Inclusion Criteria (the sponsor may add additional criteria)
 - a. Male or nonpregnant female aged 18 and older.
 - b. For women of childbearing potential, use of an effective contraceptive method for at least 1 month prior to study initiation, and maintained for the study duration.
 - c. Oropharyngeal candidiasis diagnosed at baseline by:
 - i. Clinical examination (erythema, thrush, mucositis) with or without associated symptoms (odynophagia, burning/soreness, xerostomia, modified taste, pharyngeal irritation) and
 - ii. Microbial confirmation of buccal swab (detection of candida by positive KOH AND fungal culture results).
 - d. Documented HIV seropositivity.
 - e. If subject on antiretroviral treatment at screening, on stable antiretroviral treatment for at least 2 months (or 1 month in case of treatment modification for reasons other than efficacy).
 - f. Eastern Cooperative Oncology Group (ECOG) grade less than 2.
 - g. Able to give informed consent and follow study protocol.
4. Exclusion Criteria (the sponsor may add additional criteria)
 - a. Pregnant or breastfeeding.
 - b. Milk allergy or known hypersensitivity to one of the components of the products.
 - c. Full or partial upper dentures with an acrylic border in the canine fossa.
 - d. Unable to understand consent or follow study protocol.
 - e. Has platelet count <100,000.
 - f. Hepatocellular deficiency (INR >1.7, AST and ALT > 5X normal).
 - g. Systemic candidiasis or esophageal candidiasis documented by esophageal endoscopy.
 - h. Presence of only perioral lesions, e.g., angular cheilitis.
 - i. Received systemic antifungals within past 15 days or local antifungals within past 7 days.
 - j. Hereditary galactose intolerance, lactase enzyme deficiency or glucose/galactose malabsorption.
 - k. Has received any investigational therapy within 30 days prior to randomization.
 - l. History of intolerance (e.g., elevation of liver enzymes) or sensitivity to miconazole (or other imidazole or azole compounds) or any constituent of Oravig® or unable to tolerate oral medication.
 - m. Receiving antibiotics at screening visit (prophylactic antibiotics used in the management of HIV infection and/or treatment of tuberculosis are allowed).
 - n. Life expectancy under 45 days.
5. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
 - a. Concomitant treatment with the potential to interact with miconazole: antiarrhythmics (verapamil, diltiazem, propranolol, amiodarone, atenolol, metoprolol, sotalol, dofetilide, moricizine, mexiletine, disopyramide, procainamide, quinidine gluconate or sulfate, propafenone, flecainide, tocanide), anticoagulants (anti-vitamin K: acenocoumarol and warfarin), sulfonyleurea oral hypoglycemics, astemizole, cisapride, and phenytoin.
 - b. Any treatment for oropharyngeal candidiasis, other than assigned study product.

- c. Subjects not on antiretroviral therapy at study entry must be prematurely discontinued if they need to initiate antiretroviral therapy during study treatment period.
 - d. Subjects are not to chew gum.
6. The recommended primary endpoint of this study is the proportion of subjects with a clinical cure at the test- of- cure (TOC) visit on Day 21 (i.e., 7 days after completion of 14 days of treatment) +/- 4 days in the Per Protocol analysis population. A clinical cure is defined as complete resolution of all signs and symptoms of oropharyngeal candidiasis.
 7. The following secondary endpoints may be considered for this study:
 - a. Clinical cure following 7 days of treatment (Day 8).
 - b. Clinical success (clinical cure or clinical improvement) at day 8, day 15, and TOC visit.
 - i. Clinical cure: complete resolution of lesions and symptoms: lesion score 0 and symptom score 0.
 - ii. Clinical improvement: no visible lesions (lesion score 0), and minimal symptoms (symptoms score less than 2).
 - c. Mycological cure (both negative KOH and negative fungal culture) at TOC visit.
 8. Score the oral lesions and specific signs and symptoms of oropharyngeal candidiasis at each visit using the following two scoring systems:
 - a. Oral lesions score (Murray scale)
 - 0=none
 - 1=single, localized
 - 2=multiple, localized
 - 3=extensive, confluent
 - b. Signs and Symptoms score (e.g., erythema, thrush, mucositis, odynophagia, burning/soreness, xerostomia, modified taste, pharyngeal irritation)
 - 0=absent
 - 1=mild
 - 2=moderate
 - 3=severe
 9. Any subject with worsening symptoms prior to Day 21 is to be discontinued from the study, analyzed as a treatment failure, and provided with effective therapy.
 10. At day 8, evaluate subjects for clinical success (i.e., clinical cure or clinical improvement). If the subject has not improved, he/she is to be discontinued from the study, analyzed as a treatment failure, and provided with effective therapy.
 11. At day 15, evaluate subjects for clinical success (i.e., clinical cure or clinical improvement).
 12. At day 21 (TOC visit), evaluate subjects for clinical success (i.e., clinical cure or clinical improvement) and obtain a buccal fungal culture.
 13. Perform subgroup analysis of fungal culture species to determine whether or not there was a balanced distribution of *Candida* species between treatment groups at baseline.
 14. Compare treatment compliance, duration of tablet adhesion and tablet replacement between products. For buccal tablet adhesion, compare the following individual parameters between products:
 - a. Number of tablets taken

- b. Number of tablets replaced
 - c. Number of tablets swallowed
 - d. Number of tablets spat out
 - e. Number of tablets adhering at least 6 hours
 - f. Number of tablets adhering at least 12 hours
 - g. Number of tablets adhering at bedtime
 - h. Number of subjects with adherence at least 6 hours
 - i. Number of subjects with adherence at least 12 hours
 - j. Number of subjects with adherence until bedtime
15. A statistical analysis should be conducted to show that the test product is not worse than the reference product with regards to the adherence of buccal tablet. Mean duration of adhesion and percent dislodgment within the first 6 hour after tablet placement of the test product should not be inferior to those of the RLD.
16. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
- a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who apply a pre-specified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss the scheduled applications for more than 3 consecutive days, and complete the evaluation within the designated visit window (+/- 4 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.
 - b. The mITT population includes all randomized subjects who meet the inclusion/exclusion criteria, apply at least one dose of assigned product and return for at least one post-baseline evaluation visit.
 - c. The safety population includes all randomized subjects who receive study product.
17. Subjects who are discontinued early from the study due to lack of treatment effect after completing 7 days of treatment should be included in the PP population as treatment failures. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of oropharyngeal candidiasis during the study should be discontinued, included in the PP population analysis, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).
18. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.
19. 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, severity, relation to study medication, action taken, outcome 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.
20. All local adverse events related to the application of the study treatment should be evaluated between products.
21. If the inactive ingredients of the test product are different than those contained in the RLD or in significantly different amounts, then the sponsor must 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.

22. 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.
23. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test and reference products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.
24. 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.
25. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
26. To establish bioequivalence, the equivalence interval of the test – reference difference between products for the primary endpoint (proportion of subjects with complete resolution of all signs and symptoms of oropharyngeal candidiasis) at day 21 (TOC visit) must be contained within [-0.20, +0.20] for dichotomous variables (cure versus failure) using the PP population.
27. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (cure/failure):

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the equivalence interval for the difference in success proportions between test and reference treatment must 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 and p_R = cure rate of reference treatment.

Let

n_T = sample size of test treatment group

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

n_R = sample size of reference treatment group

$c n_R$ = number of cured subjects 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 equivalence 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.

28. Study data should be submitted to the OGD in electronic format.
 - a. A list of file names, with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
 - 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, covering all variables collected in the Case Report Forms (CRFs) per subject, 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 such as demographics, signs and symptoms, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.
29. 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
- i. Duration of Treatment (total exposure in days)
- j. Completed the study (yes/no)
- k. Reason for premature discontinuation of subject
- l. Subject required additional treatment for oropharyngeal candidiasis due to unsatisfactory treatment response (yes/no)
- m. Per Protocol (PP) population inclusion (yes/no)
- n. Reason for exclusion from PP population
- o. Modified Intent to Treat (mITT) population inclusion (yes/no)
- p. Reason for exclusion from mITT population
- q. Safety population inclusion (yes/no)
- r. Reason for exclusion from Safety population
- s. Candida species isolated at baseline (yes/no)
- t. Clinical Cure (yes/no) at Day 21 visit
- u. Mycological Cure (yes/no) at Day 21 visit
- v. Treatment Compliance: number of missed doses per subject
- w. Concomitant medication (yes/no)
- x. 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	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safe_rs
101	1	01	21	YEARS	F	1	A	56	Y		N	Y		Y		Y	
101	2	01	30	YEARS	F	1	B	56	Y		N	Y		Y		Y	

can_bsse	cl_cure	my_cure	complan	CM	AE
Y	Y	Y	0	Y	Y
Y	N	N	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 Final dated 11/12/08.

STUDYID: Study Identifier

SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., M=Male, F=Female, U=Unknown
RACE:	Race, e.g., 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 control
EXDUR:	Duration of Treatment (total exposure in days)
completed:	Subject completed the study, e.g., Y=Yes, N=No
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt:	Subject required additional treatment for oropharyngeal candidiasis due to unsatisfactory treatment response, e.g., Y=Yes, N=No
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=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=Yes, N=No
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
can_base:	Candida species isolated at baseline, e.g., Y=Yes, N=No
cl_cure:	Clinical Cure at Day 21 visit, e.g., Y=Yes, N=No
my_cure:	Mycological Cure at Day 21 visit, e.g., Y=Yes, N=No
complan:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

30. Please provide a dataset containing a separate line listing for visit per subject (if data exist) using the following headers, if applicable:
- Study identifier
 - Subject identifier
 - Name of Actual Treatment (exposure): test product, RLD
 - Visit number
 - Visit date
 - Number of days since baseline visit
 - Evaluator: identity of evaluator
 - Score of oral lesions (0-3)
 - Score of each clinical sign and symptom, e.g., erythema, thrush, mucositis, odynophagia, burning/soreness, xerostomia, modified taste, pharyngeal irritation (0-3)
 - KOH microscopic evaluation (positive or negative)
 - Mycological culture result (positive or negative)
 - Concomitant medication reported during this visit (yes/no)
 - Adverse event reported 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	score_le	score_er	score_th	score_mu	score_od	score_bu	score_xe	score_mo	score_ph	koh	my_cult	CMrpt	AErpt
101	1	A	1	2004-07-01	1													Y	Y

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 Final dated 11/12/08.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
EXTRT: Name of Actual Treatment (exposure), e.g., A=test product, B=RLD
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
score_le: Score of oral lesions, e.g., 0-3
score_er: Score of erythema, e.g., 0-3
score_th: Score of thrush, e.g., 0-3
score_mu: Score of mucositis, e.g., 0-3
score_od: Score of odynphagia, e.g., 0-3
score_bu: Score of burning/soreness, e.g., 0-3
score_xe: Score of xerostomia, e.g., 0-3
score_mo: Score of modified taste, e.g., 0-3
score_ph: Score of pharyngeal irritation, e.g., 0-3
koh: KOH microscopic evaluation, e.g., P=positive, N=negative)
my_cult: Mycological culture result, e.g., P=positive, N=negative)
CMrpt: Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
AErpt: Adverse Event reported during this visit, e.g., Y=Yes, N=No

31. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of miconazole.