

Draft Guidance on Miconazole

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Tablet; Buccal

Recommended Studies: One study

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

Design: Randomized, double blind, parallel, in vivo

Strength: 50 mg

Subjects: Males and nonpregnant, nonlactating 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: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. 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 abbreviated new drug application (ANDA).

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. 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.
3. 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.
4. 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, flecanide, 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.
 5. 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 (oral lesion score =0, signs and symptoms score =0).
 6. 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
 7. 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.
 8. 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.

9. At Day 15, evaluate subjects for clinical success (i.e., clinical cure or clinical improvement).
10. At Day 21 (TOC visit), evaluate subjects for clinical success (i.e., clinical cure or clinical improvement) and obtain a buccal fungal culture.
11. 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.
12. 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
13. 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.
14. All local adverse events related to the application of the study treatment should be evaluated between products.
15. 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
16. 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>