Contains Nonbinding Recommendations

Draft Guidance on Oxiconazole Nitrate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Cream/Topical

Recommended studies: 1 study

Type of study: Bioequivalence (BE) Study with Clinical Endpoint
Design: Randomized, double blind, parallel, placebo-controlled in vivo
Strength: EQ 1% Base
Subjects: Healthy males and females with tinea pedis
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 study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends a BE study with clinical endpoint in the treatment of tinea pedis. Subjects are to be randomized to receive the generic oxiconazole nitrate topical cream, EQ 1% Base, the reference listed drug (RLD), or placebo. Sufficient study drug is to be applied to cover affected and immediate surrounding areas once daily for 28 consecutive days (i.e., 4 weeks). The primary endpoint is to be evaluated at the test-of-cure visit (study Week 6, two weeks after the end of treatment).

2. Although all tinea pedis lesions on both feet are to be treated in this study, a target lesion on one foot is to be identified as the most severe lesion and evaluated at the baseline visit and at each study visit. Score each of the following signs and symptoms using the following scale:
   a. **Signs**: fissuring/cracking, erythema, maceration, and scaling
   b. **Symptoms**: pruritus and burning/stinging
   c. **Scoring Scale**: Each score should be objectively defined. The following is an example of an acceptable scale.

      0 = none (complete absence of any signs or symptoms)
      1 = mild (slight)
      2 = moderate (definitely present)
      3 = severe (marked, intense)

3. Inclusion Criteria (the sponsor may add additional criteria):
   a. Healthy males and females aged ≥ 18 years.
   b. Clinical diagnosis of tinea pedis with lesions localized to the interdigital spaces or predominantly interdigital, but may extend to other areas of the foot (the non-interdigital lesions should not be hyperkeratotic, i.e., characteristic of tinea pedis moccasin), and provisionally confirmed at baseline by a positive potassium hydroxide (KOH) wet mount preparation (i.e., skin scrapings from the target site are placed on a microscope slide with a drop of 10% KOH, and microscopic examination reveals segmented fungal hyphae).
   c. The sum of the clinical signs and symptoms scores of the target lesion is at least 4, including a minimum score of at least 2 for erythema AND a minimum score of 2 for either scaling or pruritus (on a scale of 0-3, where 2 indicates moderate severity).

4. Exclusion Criteria (the sponsor may add additional criteria):
   a. Pregnant or lactating or planning to become pregnant during the study period.
   b. Use of antipruritics, including antihistamines, within 72 hours prior to entry into the study.
   c. Use of topical corticosteroid, antibiotics or antifungal therapy within 2 weeks prior to entry into the study.
   d. Use of systemic (e.g., oral or injectable) corticosteroid, antibiotics or antifungal therapy within 1 month prior to entry into the study.
   e. Use of oral terbinafine or itraconazole within 2 months prior to entry into the study.
   f. Use of immunosuppressive medication or radiation therapy within 3 months prior to entry into the study.
   g. Confluent, diffuse moccasin-type tinea pedis of the entire plantar surface.
   h. Presence of any other infection of the foot or other disease process that might confound the treatment evaluation.
   i. History of dermatophyte infections unresponsive to systemic or topical antifungal drugs.
   j. Known hypersensitivity to oxiconazole nitrate or to any component of the formulations.

5. A positive skin 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 skin fungal culture must be obtained at baseline at the target site. Testing should be performed to identify the isolates at the species level (e.g., *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum*). Only subjects with a pretreatment baseline skin fungal culture from the target site that is positive for *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum* should be included in the per protocol (PP) and modified intent to treat (mITT) populations for the primary endpoint analysis. Subjects with a negative baseline fungal culture should be excluded from the PP and mITT populations, but included in the safety population for the safety analyses.

6. *Trichophyton rubrum* is the most common infecting organism in tinea pedis. Therefore, > 50% of the subjects should have fungal cultures positive for *T. rubrum* upon entry into the study.

7. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
   a. Any other topical products applied to the target site
   b. Systemic (e.g., oral or injectable) antibiotics or antifungals.
   c. Systemic corticosteroid or immunosuppressive drugs.
   d. Antipruritics, including antihistamines, within 24 hours of study visits.

8. The recommended primary endpoint of the study is the proportion of subjects with therapeutic cure, defined as both mycological cure and clinical cure, at the test-of-cure visit conducted 2 weeks (+/- 4 days) after the end of treatment (study Day 38-46). Mycological cure is defined as a

negative KOH test AND a negative fungal culture. Clinical cure is defined as a total severity score no more than 2 with no individual severity score greater than 1, on a 4-point scale provided above.

9. The protocol should clearly define the PP, mITT and safety populations:
   a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, had a positive baseline skin fungal culture for *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum,* were compliant with the assigned study treatment, and completed the evaluation at the test-of-cure visit within the designated visit window (+/- 4 days; i.e., study Day 38-46). The protocol should provide a definition of compliant subjects (e.g., 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 subject diaries).
   b. The mITT population includes all randomized subjects who met the inclusion/exclusion criteria, had a positive baseline skin fungal culture for *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum,* used at least one dose of study product, and returned for at least one post-baseline visit.
   c. The safety population includes all randomized subjects who received study product.

10. Subjects who are discontinued early from the study due to lack of treatment effect after completing 14 days of treatment should be included in the mITT and PP population as treatment failures. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF.

11. Subjects who receive or self-administer topical drug therapy to the feet for the treatment of irritation/pruritus after the treatment phase of the study should be analyzed in the mITT and PP populations as a treatment failure.

12. 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.

13. 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.

14. 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.

15. 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 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.

16. 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.

17. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

18. 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 38-46) must be within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP population.

19. As a parameter for determining adequate 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 38-46), using the mITT study population and Last Observation Carried Forward (LOCF).

20. 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 must be contained within [-0.20, +0.20] in order to establish equivalence.

    The compound hypothesis to be tested is:

    H_0: $p_T - p_R < -0.20$ 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

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

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

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

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

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

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.

21. 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.
    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 such as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

22. 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 subject
    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	complian	CM	AE
101	1	01	22	YEARS	F	1	A	28	Y		Y		Y		N	0	Y	Y
101	2	01	30	YEARS	F	1	B	28	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 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
EXDUR:	Duration of Treatment (total exposure in days)
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, B=negative baseline culture, 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.
cure:	Final designation e.g., Y=Yes (therapeutic cure), N=No (failure)
complian:	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

23. 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. Fissuring/Cracking score
    i. Erythema score

j. Maceration score
k. Scaling score
l. Pruritus score
m. Burning/Stinging score
n. Composite (total) 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	fisscrac	erythema	macerati	scaling	pruritus	burnstin	compss	koh	culture	mycocure	clincure	thercure	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	0	JB	0	2	1	2	0	0	5	Pos	Pos				Y	N	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, C= placebo control
VISITNUM:	Visit Sequence Number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed Time since Baseline (days)
EVAL:	Evaluator: identity of the evaluator, e.g., initials
fisscrac:	Fissuring/Cracking score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
erythema:	Erythema score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
macerati:	Maceration score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
scaling:	Scaling score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
pruritus:	Pruritus score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
burnstin:	Burning/Stinging score, e.g., 0=none (complete absence, 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
compss:	Composite (total) signs and symptoms score
koh:	KOH, e.g., Pos=Positive, Neg=Negative

culture:	Culture result, e.g., A=Positive for *T. rubrum*, B=Positive for *T. mentagrophytes*, C=Positive for *E. floccosum*, D=Positive for other organism, E=No growth
mycocure:	Mycological cure, e.g., Y=Yes, N=No
clincure:	Clinical cure, e.g., Y=Yes, N=No
thercure:	Therapeutic cure, e.g., Y=Yes, N=No
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
LBtest:	Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

24. 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 oxiconazole nitrate.