Contains Nonbinding Recommendations

Draft Guidance on Ketoconazole Shampoo

Active ingredient: Ketoconazole USP, 2%

Form/Route: Shampoo (Suspension)/Topical

Recommended studies: Clinical Endpoint Bioequivalence Study

Bioequivalence study recommendations:

1. A bioequivalence study with a clinical endpoint in the treatment of tinea versicolor is recommended for ketoconazole shampoo, 2%. The study should be a randomized, double-blind, placebo controlled, parallel design, study in subjects with tinea versicolor. Subjects who meet inclusion/exclusion criteria should be randomly assigned to treatment with test, reference or placebo. Subjects should be instructed to use a single application of the shampoo on the infected and surrounding areas of the body on a single occasion as directed in the product labeling. Subjects should be evaluated at baseline (Day 0), at an interim visit on Day 7, and at Day 28.

2. It is important to establish and document the diagnosis of tinea versicolor at baseline. To ensure adequate sensitivity of the study to detect differences between products, the study must enroll subjects with sufficient severity of disease to allow for a definite treatment effect. The inclusion criteria should therefore include subjects with a clinical diagnosis of tinea versicolor AND both of the following:

    - A combined severity score of at least 4, with at least one of the following signs and symptoms rated at least 2, using the following scale:

Signs/symptoms	**Scale**
desquamation/scaling pruritis/itching erythema	0 = absent 1 = mild 2 = moderate 3 = severe

    - Presence of infection with *Malassezia furfur (Pityrosporum orbiculare or P. ovale)* confirmed by a positive KOH cellophane tape test showing the characteristic “spaghetti and meatballs” appearance of the round budding yeast cells and short hyphae.

3. The categories mild, moderate, and severe on the above signs and symptoms scoring scale, should be clearly defined for each of the signs and symptoms with an objective description.

When evaluating signs and symptoms, the entire body should be evaluated. A Baseline Body Diagram may be helpful for location.

4. A Physician's Global Assessment (PGA) should also be incorporated into the assessment. The evaluation should be a static scale, describing the severity of lesions associated with each score. This scale should not be an assessment of treatment response, but should clearly describe the condition at the time of each visit. Therefore, no reference should be made to baseline in the evaluation. The following is an example of a scale that could be used:

   0 = clear; no scaling, itching or erythema
   1 = mild scaling, limited distribution, with or without itching and with or without erythema
   2 = moderate scaling, with or without itching
   3 = severe, extensive distribution of scaling, with or without itching

   Mild, moderate, and severe should be objectively defined.

   A score of "0 = clear" would be considered a "success."

5. The use of shampoos and soaps during the study needs to be addressed and clearly explained to the Subjects. It is recommended that only shampoos and soaps that are non-medicated are used during the entire study period (through Day 28) and that the products are approved by the investigator prior to study initiation.

6. In order to aid in fungal detection, subjects should be instructed not to bathe or shower prior to each visit.

7. 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 expected effect size for treatment with the reference product and the expected variability in response. The power of the study should be based on the primary endpoint.

8. The primary endpoint for this product is the proportion of subjects with treatment success/cure at the Day 28 visit. To establish bioequivalence, the 90% confidence interval of the difference between products for the primary endpoint (success proportion) must be within (-0.20, +0.20) for dichotomous variables (cure versus failure) using the Per-Protocol (PP) population for analysis. It is important that overall success be defined in terms of mycology, clinical signs and symptoms score, and the PGA *a priori*. For example:

   Success should be defined as:
   A negative cellophane tape test (absence of hyphae); and
   A PGA score of "clear"; and
   A severity score of 0 for erythema, and 0 for pruritis/itching, and 0 for scaling/desquamation

   Failure should be defined as:

A positive cellophane tape test (presence of hyphae); or
A PGA score other than "clear"; or
A severity score on the clinical signs and symptoms of one or greater for erythema or pruritis/itching or scaling/desquamation.

9. 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 success rates between test and reference treatment should be contained within (-.20, +.20) in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R \leq -.20$ or $p_T - p_R \geq .20$

versus

H_A: $-.20 < p_T - p_R < .20$

where:
p_T = success/cure rate of test treatment group
p_R = success/cure rate of reference treatment group

Let
n_T = sample size of test treatment group
$c n_T$ = number of success/cured Subjects in test treatment group
n_R = sample size of reference treatment group
$c n_R$ = number of success/cured Subjects in reference treatment group

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

and se = $(\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{½}$.

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 $L \geq -.20$ and $U \leq .20$

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

10. In order to demonstrate that the study is sufficiently sensitive to show a difference between products, both test and reference products should be statistically superior to placebo ($p < 0.05$, two sided) in the overall success rate at Visit 3 (day 28), using a defined intent-to-treat (ITT) population.

11. It is recommended that the randomization code be generated by an independent third party, (or by the sponsor only if not involved in packaging and labeling of study medication) in order to decrease the chance of unblinding and to minimize bias.

12. 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 verification of the treatment identity for each patient.

13. In the packaging of both the bottle and the outer containers, 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. Neither the subject nor the investigator should be able to identify the treatment. A detailed description of the blinding procedure should be provided in the protocol.

14. Refer to 21 CFR 320.38 and 320.63 regarding retention of study drug samples. For more information, 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."

15. The safety population should include all subjects that received study medication.

16. The Intent-To-Treat (ITT) subject population should be clearly defined. This population should include those subjects who meet all inclusion/exclusion criteria, have received study medication and who have returned for at least one post-baseline visit.

17. The Per-Protocol (PP) population should also be clearly defined. It should consist of all randomized subjects 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) unless discontinued from the study as a treatment failure or

required additional treatment for the same condition, and did not have any protocol violations.

18. Subjects compliance should be clearly defined a priori (e.g., for this study, compliant subjects may be defined as having used a single application of the product as recommended and not having used restricted medications).

19. Subjects that are discontinued from the study after the interim visit because of lack of treatment effect or worsening of the disease should be included in the PP population as treatment failures, using Last Observation Carried Forward (LOCF). Subjects discontinued for other reasons should be excluded from the PP population, but included in the ITT population, using LOCF.

20. For clinical endpoint bioequivalence studies of topical 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 the expected AEs as well as unexpected AEs. The protocol must include a provision to compare the test and reference product with regard to the occurrence and severity of drug-related AEs. The safety analyses should include all subjects who received a dose of study medication.

21. Study data should be submitted to the OGD in electronic format. 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. 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). Please refer to the Guidance for Industry, "Regulatory Submissions in Electronic Format; General Considerations" (January 1999) at http://www.fda.gov/cder/guidance/2867fnl.pdf. 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, and an explanation of the format for each SAS variable should be included.

    Primary datasets should consist of two datasets: No Last Observation Carried Forward (NO-LOCF – pure dataset) and Last Observation Carried Forward (LOCF – modified dataset). Per each patient, the following variables should be contained in the datasets:

        Center/site, 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 ITT population, PP population (yes/no), reason for exclusion from PP population, baseline severity (signs/symptoms score, PGA), overall outcome (success/failure)

    Per each visit including baseline visit if data exist per each subject, the following variables should be contained in the datasets:

Visit number, date of visit, visit days from baseline, reason for exclusion from ITT per visit, reason for exclusion from PP per visit, individual sign/symptom scores, total score, cellophane tape test (+/-), KOH (if applicable), PGA score, overall success (y/n), adverse events, reason for discontinuation.

The methods used to derive the variables such as ITT, PP, success or failure for dichotomized PGA, etc., should be included and explained.

Secondary datasets: SAS transport files should cover all variables collected in the Case Report Forms (CRF) per patient. We request a single file for each field such as demographics, baseline admission criteria and vital variables, clinical variables per each visit plus visit date, adverse events, reasons for discontinuation of treatment, medical history, compliance and comments, etc.

22. For all topical products, if the inactive ingredients are different than those contained in the RLD or in different amounts, 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 product.

23. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other strength of ketoconazole shampoo.

24. This information represents the best judgment of the FDA at this time and is subject to change in the future. Sponsors may submit protocols for review and comment to the Clinical Review Team, Office of Generic Drugs prior to conducting bioequivalence studies with clinical endpoints.