CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-581

MEDICAL REVIEW

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Medical Officer Review
July 27, 1999

ANDA 75-581
Drug Product: Ketoconazole 2% Cream
Firm: TEVA Pharmaceuticals USA
Reference Listed Drug: Nizoral Cream 2%, Janssen Pharmaceutica

Composition

Ketoconazole	20 mg/g
Propylene Glycol	
Cetyl Alcohol NF	
Stearyl Alcohol NF	
Isopropyl Myristate NF	
Sorbitan Monostearate NF	
Polysorbate	
Polysorbate	
Sodium Sulfite,	
Purified Water,	

Protocol # 95-01

Title A Multicenter, Double-Blind, Three-Way, Parallel Study Comparing the Bioequivalence of Two Formulations of Ketoconazole Cream, 2% and a Placebo Cream in the Treatment of Tinea Pedis

Study Period - 7/28/97 - 11/12/98

Background

The study was designed based on the 1990 Draft Guidance for the performance of a Bioequivalence Study for Topical Antifungal Products under IND 15-295. The protocol was modified following comments from the FDA. A revised protocol was submitted on 8/25/97 including patients with moccasin-type tinea pedis. Another revision was submitted 9/23/97 to clarify the definition of cure, change the sample size due to the inclusion of moccasin-type tinea pedis, change the number of investigators, and provide

stratification for moccasin-type and non-moccasin-type tinea pedis.

The sponsor conducted an audit of the sites on a "for cause" basis and identified one site where there were concerns about GCP procedure. This site was discontinued. OGD was informed of this decision and asked to evaluate a plan to redistribute the remaining drug supply.

Objectives

To compare the safety, bioequivalence, and efficacy of ketoconazole 2% cream manufactured by TEVA Pharmaceuticals USA, Nizoral 2% Cream manufactured by Janssen Pharmaceutica and Vehicle cream (without ketoconazole) manufactured by TEVA Pharmaceuticals USA, in the treatment of patients with tinea pedis.

Investigators

There were 18 centers that participated in the study. They are listed below in numerical order:

Terry Jones	Bryan TX
Lawrence Parish	Philadelphia PA
Debra Breneman	Cincinnati OH
Lee Lumpkin	San Antonio TX
Robert Skinner	Memphis TN
Mark Ling	Atlanta GA
Larry Millikan	New Orleans LA
Edgar B. Smith	Galveston TX
David Fivenson	Detroit MI
Sewon Kang	Ann Arbor MI
Steven Kempers	Fridley MN
Jon Hanifin	Portland OR
Stephen Kraus	Atlanta GA
John Humniuk	Greer SC
Toni Funicella	Austin TX
Gary Heller	St. Petersburg FL
Nlsd Tryrd	Miami FL
Michael Scannon	Tampa FL

A central laboratory was used for the mycologic, hematologic, chemistry and urine testing.

Study Design

This was a double-blind, placebo-controlled, multicenter, randomized, parallel group, comparative study with three study arms: ketoconazole (TEVA) 2% cream (test), Nizoral 2% cream (reference), and vehicle (TEVA) (placebo). Patients with moderate to severe symptoms and signs of interdigital or moccasin-type tinea pedis were enrolled following screening for clinical and laboratory parameters including a positive KOH of skin scraping. A skin scraping sample was sent at baseline and a positive culture for one of *T. rubrum, T. mentagrophytes,* or *E. floccosum* was necessary for the patient to be retained in the Intent-to-Treat group. Treatment was for 42 days and patients were followed for an additional 2 weeks. The primary outcome was clinical and mycological cure at the 2 week post-treatment visit.

Study Visits

Visit 1 (Day 1) Screening/Initiation

At the first visit patients had a complete history, physical examination, evaluation of tinea pedis signs and symptoms, collection of samples for KOH, fungal culture, urinalysis, pregnancy test (if applicable), and other laboratory tests. Patient diaries, medications, and instructions were given to eligible patients.

Visit 2 (Day 22 +/- 5, Week 3)

Visit 3 (Day 43 +/- 5, Week 6)

At follow-up visits patient compliance, adverse events, and concomitant medications were reviewed. Clinical signs and symptoms were recorded, a KOH test was done and a fungal culture sample was collected. At week 3 and 6 unused medication was collected. At week 3, laboratory tests, including pregnancy test if applicable, were done and new medication was dispensed.

Visit 4 (Day 57, Week 8, 11-21 days after stopping treatment)

The evaluation outlined above was completed at this visit.

Inclusion Criteria

1. Males or females at least 18 years of age and in general good health as determined by a medical examination and medical history, with no known medical conditions or use of other medication that may have interfered with study participation.
2. Patients with a clinical diagnosis of moderate to severe symptomatic tinea pedis with at least one symptom and two primary signs of tinea pedis, each of which was rated as moderate or severe and involved the interdigital spaces of the foot/feet.
3. The patient should have had uncomplicated tinea pedis with no signs of a bacterial infection or other condition(s) that would interfere with his/her clinical evaluation during the course of the study.
4. Patients with a positive KOH microscopic examination were presumptively enrolled at baseline pending confirmation of a positive dermatophyte microorganism identified on fungal culture (*T.rubrum, T. mentagrophytes,* and/or *E. floccosum*).
5. Female patients of child-bearing potential must have used or agreed to use a reliable method of contraception throughout the study (e.g., condom with spermacide, IUD with spermacide, abstinence, oral contraceptives or partner's vasectomy) and must not have been pregnant as determined by a pregnancy test at screening.
6. Female patients taking oral contraceptives must have been on the same product for a minimum of 3 months and must have agreed to continue taking the same product for the entire course of the study.
7. Use of all topical antifungals and other topical products for the feet must have been discontinued at least two weeks prior to study entry (8 weeks for Naftin® Cream, Mentax® Cream, or Lamisil® Cream); all systemic antifungal and/or steroid therapy must have been discontinued at least four weeks prior to study entry (3 months for Diflucan®, Sporonox® or Lamisil® Tablets).
8. Patients were to agree to maintain personal foot hygiene throughtout the study and to comply with all requirements of the protocol.
9. Patients must have had the study fully explained to them and signed and dated an approved informed consent

document prior to initiating any study related procedures.

Exclusion Criteria

1. Patients experiencing any other dermatoses or skin conditions of the feet that may have interfered with the evaluation of tinea pedis.
2. Patients with known hypersensitivity to ketoconazole, other imidazole antifungal agents, or any component of the test formulations, particularly sulfiltes.
3. Patients who had used topical antifungals and/or topical products for the feet within two weeks prior to study entry (within 8 weeks for Naftin® Cream, Mentax® Cream, or Lamisil® Cream), or systemic steroid and/or antifungal therapy in the 4 weeks preceding study entry (within 3 months for Diflucan®, Sporonox®, or Lamisil® Tablets).
4. Female patients who were pregnant or lactating, who wanted to become pregnant during the study period or who refused to use an approved method of birth control.
5. Patients who had used another investigative drug while participating in another investigative trial within the previous 30 days.
6. Patients with any known unstable chronic illness including cardiovascular, hepatic, renal, neurologic, endocrine, gastrointestinal, or CNS disorder.
7. Patients with recurrent tinea pedis which had been unresponsive to previous prescription antifungal treatment, including other antifungal formulations containing ketoconazole as the active ingredient.
8. Patients with known diabetes mellitus (Type I or Type II) that was not controlled by diet.
9. Patients diagnosed with HIV or any patients who were on immunosuppressant therapy or were known to have an impaired immune system.
10. Patients who, in the opinion of the investigator, would be non-compliant with the protocol.

Randomization

An independent contractor provided the computer-generated scheme in blocks of 6 for each center. The only individual who was unblinded was the statistician at Hurley who created the randomization schedule. Patients were assigned unique, sequential numbers not previously assigned to

another subject. The procedures described for maintaining blinding were acceptable.

Medications

A 60 gram tube of study medication was dispensed to the patient and they were instructed on proper use and application of the product. Medications dispensed for each group were as follows:

Test Product: Ketoconazole 2% Cream, TEVA Pharmaceuticals USA - 60 gm tube, Lot #0479-100, Expiration date 11/98

Reference Product: Nizoral® 2% Cream, Janssen Pharmaceutica - 60 gm tube, Lot #96M675E, Expiration date 11/98

Placebo: Vehicle Cream, TEVA Pharmaceuticals USA - 60 gm tube, Lot #0479-153, Expiration date N/A

Patients also received a study diary and instructions on self-scoring of clinical signs and/or symptoms.

All other topical antifungals and other topical products for the feet must have been discontinued as outlined in the inclusion/exclusion criteria. All topical and systemic antifungals were prohibited during the study. No other topical foot products were permitted.

Compliance

Patient compliance was monitored at each study visit by questioning patients, reviewing their diaries for missed doses, and sending the unused tubes to Covance Pharmaceutical Packaging Services for weighing.

A Priori criteria for Premature Discontinuation

Patients were discontinued from the study for the following reasons:

1. Voluntary withdrawal
2. Adverse event
3. Non-compliance with study procedures
4. Failure to return for study visits(s)
5. More than two missed doses in any treatment week

6. Use of contraindicated concomitant medication
7. Treatment failure sufficient to require treatment prior to the planned completion of the study
8. Pregnancy
9. Negative fungal culture at the baseline visit
10. Investigator's judgement that continued treatment was not in the interest of the patient

Only patients discontinued for a serious adverse event were followed after termination. These patients were followed until all parameters were normal or explained.

Endpoints

The primary determination of bioequivalence and efficacy was made by comparing overall treatment success based on combined clinical and mycological cure data from the 2-week post treatment (Week 8) visit in the Intent-To-Treat cohort using last observation carried forward for missing values. Data obtained at the end-of-treatment (Week 6) visit was considered a secondary endpoint. A mycological cure was defined as a culture negative for dermatophyte growth and a negative KOH microscopic examination. A clinical cure was defined as resolution of the signs and symptoms of tinea pedis infection, such that in the medical opinion of the investigator, the patient required no additional antifungal treatment.

Medical Officer Note: The determination of efficacy of both test and reference drugs compared to placebo is carried out using the ITT population. However, the determination of bioequivalence is based on the endpoint in the Per Protocol population.

Safety

Safety was evaluated by eliciting patient history for symptoms and adverse events, examining the subject, and reviewing laboratory testing.

Data Quality Assurance

Investigator training was conducted prior to study initiation and during the study, especially after the addition of new sites. A centralized lab was used for all laboratory testing. Contract organizations were used for statistical analysis, study medication packaging,

monitoring, and study site audits.

audited ten of the 18 study sites. Sites were chosen either based on patient enrollment or "for cause" based on concerns from the monitors. At one study site (#007), significant issues related to GCP procedures were identified. Patients were seen for an immediate follow-up visit and the enrollment at this center was terminated. It was felt that the data generated at this site was valid and could be included in the analysis. The clinical database was audited by the group by validating 100% of all primary endpoints and safety information for 25% of the case report forms of patients in the database.

Sample Size and Statistical Plan

Sample size calculations and a statistical plan were outlined in the protocol that was reviewed by the Agency. These were modified during the study in order to include a group of patients with moccasin-type tinea pedis. These procedures and their subsequent changes will be evaluated during the Statistician's review that will be a companion document to this one.

Populations Analyzed

Three populations were defined in the study report:

- Safety Intent-To-Treat - all enrolled patients who received study medication
- Intent-To-Treat - patients with a positive culture for *T. rubrum, T. mentagrophytes,* and/or *E. floccosum* and who applied at least one dose of study medication
- Per Protocol - all patients who met the following criteria:
  - Did not take any prohibited concomitant medication. (Patients taking inhaled steroids were not excluded from the completer analysis.)
  - The time from the first to last dose of study medication was 42+/-5 days (i.e., 37-47 days).
  - Returned for Week 8 evaluation between 11-21 days after completion of treatment.
  - Missed no more than 2 doses of study medication in any treatment week period until Week 6.

- Unless a sufficient case-by-case rationale was presented by TEVA USA, patients who did not meet the study inclusion and exclusion criteria were not included in the completer cohort.
- TEVA USA reserved the right to exclude any patient from the completer cohort based on Quality Assurance audit findings or any other issue in which the validity of patient data is in doubt.

RESULTS

Sample

The number of patients in each analysis population by treatment group is summarized in Table I.

Table I

	Ketoconazole	Nizoral	Placebo	None	Total
Screened	201	206	206	122 16.8%	728
Safety ITT	201	206	206		606 83.3%
ITT	124	121	127		372 51.1%
Per Protocol	80	92	98		270 37.1%

Of the 122 who failed screening, 112 did not meet inclusion/exclusion criteria, 3 withdrew, and 7 were classified as "other" (Four had a negative KOH, 1 had mild tinea pedis, 1 had tinea corporis, and 1 had tinea cruris.)

Of the 606 who received medication, 325 completed the study, 197 had negative screening fungal cultures, and 84 were terminated for the following reasons:

- 11 - Adverse events
- 25 - protocol violations
- 7 - patient decision to withdraw
- 25 - lost to follow-up
    - 13 never returned after randomization
- 1 - death, fire in apartment
- 15 - "other" -
    - 4 - diagnosed with diabetes mellitus, type I or II
    - 4 - visit non-compliance
    - 1 - moved away
    - 3 - laboratory abnormalities

- 1 - patient decision at Week 6

The sponsor's analysis showed no differences among the treatment groups in withdrawals and the cohort numbers presented in Table I are similar for each population and each treatment group.

Protocol Deviations

The types and number of protocol deviations for each study arm is presented in Table II. Patients with these protocol deviations were excluded from the Per Protocol analysis but included in the Intent-To-Treat group. Many patients had more than 1 deviation from the protocol.

Table II
Protocol Deviations

	Ketoconazole	Nizoral	Placebo
Did not meet # of days between 1st dose and last dose (37-47 days)	21	21	14
Did not meet # days between last dose and Week 8 (11-21 days)	36	30	23
Missed > 2 doses within any treatment week	3	4	6
Violated inclusion/ exclusion criteria	4	2	2
Missing Week 6 data	2	2	0

Among these patients were several with a positive screen who received medication and had no efficacy data (5, Ketoconazole; 7, Nizoral; and 2, Placebo).

Gender, Ethnicity, and Age

The treatment groups were balanced for age, gender, and ethnicity (Tables III and IV).

Table III
Gender and Ethnicity

	Ketoconazole	Nizoral	Placebo
Gender			
Male	45 (36.3%)	32 (26.4%)	32 (25.2%)
Female	79 (63.7%)	89 (73.6%)	95 (74.8%)

Race	Ketoconazole	Nizoral	Placebo
Asian	3 (2)	2 (2%)	2 (2%)
Black	27 (22	21 (17%)	23 (18%)
Caucasian	80 (64%)	86 (71%)	93 (73%)
Hispanic	12 (10%)	12 (10%)	8 (6%)
Other	2 (2)	0 (0%)	1 (1%)

Table IV
Age of ITT cohort per treatment group

Treatment	Number	Mean +/- SD	Range
Ketoconazole	124	40.6 +/- 13.4	19 -80
Nizoral	121	40.2 +/- 13.6	18 - 79
Placebo	127	39 +/- 13.4	18 - 72
Total	372	39.9 +/- 13.4	18 -80

History of Related Dermal Fungal Disease

The three treatment groups had a significant number of patients with a history of prior related fungal infection involving the web space, foot or toes. The distribution was equal among the three groups, however (Table V).

Table V
History of Prior Related Disease

	Ketoconazole	Nizoral	Placebo
Interdigital tinea pedis	40	43	51
Onychomychosis	3	2	1
Moccasin-type tinea pedis	5	3	1
Interdigital and onychomycosis	21	14	16
Interdigital and moccasin-type	10	13	14
Onychomycosis and moccasin-type	1	1	0
Interdigital and onychomycosis	20	21	15
No history of tinea pedis	24	19.4	29

Type of Disease and Infecting Organism

The distribution of patients with either interdigital or moccasin-type infection in the ITT cohort is presented in Table VI. Subjects are nearly equally divided among the two groups. The number of individuals infected with *T.rubrum*,

T. mentagrophytes, and/or *E. floccosum* is shown in Table VII. Most patients (87%) had infection due to *T. rubrum*.

Table VI
Distribution of study subjects with interdigital vs. moccasin-type infection in the ITT cohort

Type of tinea pedis	Ketoconazole	Nizoral	Placebo	Total
Interdigital	61 (49%)	58(48%)	68(54%)	187(50.3%)
Mocassin-type	63 (51%)	63(52%)	59(47%)	185(49.7%)

Table VII
Results of fungal culture of ITT cohort

Organism	Ketoconazole N=124	Nizoral N=121	Placebo N=127	Total N=372
T. rubrum	109	102	113	324(87%)
T. mentagrophytes	10	9	10	29(8%)
E. floccosum	5	10	4	19(5%)

Compliance

Patient diary records and patient interviews by staff at each visit were used to evaluate compliance. All patients in the Per Protocol group were by definition compliant (missed no more than 2 doses in a treatment week). In the ITT group, 13 patients were not compliant during at least one treatment week (3 on Ketoconazole, 4 on Nizoral®, and 6 on Placebo).

Efficacy

Treatment success was evaluated by both clinical and mycological cure at the Week 8 visit, two weeks post treatment. In the Intent-To-Treat cohort, 48 subjects violated visit windows. In these cases the efficacy data was reassigned to the nearest scheduled visit in those cases.
The success rates (Week 8) for the ITT and Per Protocol cohorts are presented in Table VIII. The sponsor's analysis used the ITT group for both efficacy and bioequivalence evaluations. The Per Protocol group is preferred for the bioequivalence assessment. The results of the study appear to indicate that both the test and reference drug are better than placebo and that the test and reference

products are bioequivalent. The statistician's evaluation will confirm whether the study passes the efficacy and bioequivalence criteria. The end-of-treatment (Week 6) success rates also demonstrate the same trend (Table XI).

Table VIII
Treatment success rates (Week 8) for the ITT and Per Protocol groups

	Ketoconazole	Nizoral	Placebo	Confidence Intervals
ITT	55(44.4%)	49(40.5%)	13(10.2%)	
Ketoconazole vs. Placebo				0.28-0.42
Nizoral vs. Placebo				0.42-0.42
Per Protocol	40(50%)	44(48%)	13(13%)	
Ketoconazole vs. Nizoral				-0.07-0.14

Table IX
Treatment success rates at the end of treatment (Week 6) for the ITT and Per Protocol groups

	Ketoconazole	Nizoral	Placebo	Difference between Ketoconazole and Nizoral
ITT	31(25%)	27(22%)	6(6%)	-0.01
Per Protocol	20(25%)	24(26%)	7(7%)	-0.02

The results were similar for both treatment cohorts whether a pooled center analysis was done or the test was adjusted for center differences.

Safety

Treatment duration was similar among the three groups: 39.7 +/- 7.1 days, Ketoconazole; 40.3 +/-5.9 days, Nizoral; and 40.3 +/- 5.3 days, Placebo. There were few adverse events and these were evenly distributed across the treatment groups (Table X).

Table X
All adverse events occurring in >/= 10 subjects

	Ketoconazole	Nizoral	Placebo	Total
Headache	19 (9.5%)	17(8.5%)	16(7.8%)	52
Infection	8 (4%)	7(3.5%)	12(5.8%)	27
Lab test abnormality	6 (3%)	5(2.5%)	10(4.9%)	21
Pain	9 (4.5%)	9(4.5%)	8(3.9%)	26
Pharyngitis	3 (1.5%)	4(2%)	6(2.9%)	13
Rhinitis	7 (3.5%)	7(3.5%)	8(3.9%)	22
Sinusitis	3 (1.5%)	2(1%)	5(2.4%)	10
Pruritus	4 (2%)	12(6%)	8(3.9%)	24
Rash	5 (2.5%)	10(5%)	11(5.3%)	26
Dysmenorrhea	5 (2.5%)	3(1.55)	4(1.9%)	12

Twenty-seven ADEs were judged to be either probably or definitely "related to drug". Of these, 24 affected the skin. The sponsor reports that there was no difference in the overall severity of symptoms by treatment group or gender. There were 8 serious adverse events but none were related to the study medication. These are listed below:

1. Death due to smoke inhalation from apartment fire
2. Hospitalization for COPD exacerbation
3. Elective surgery, lithotripsy for kidney stone
4. Elective arteriogram, angioplasty
5. Hospitalization for exercise-induced chest pain
6. Hospitalization for pneumonia and atrial fibrillation
7. Hospitalization for migraine headache after discontinuing study medications
8. Colon cancer and anemia

Laboratory adverse events were relatively uncommon in this study affecting 6 on Ketoconazole, 5 on Nizoral, and 11 on Placebo.

Conclusion

This study compared TEVA's ketoconazole to the reference listed drug, Nizoral, and has demonstrated that the two drug products are bioequivalent. The in vivo bioequivalence study should be consulted to the Division of Dermatologic

Drug Products for secondary review and to Statistics for a review of the statistical methods and analyis.

Mary M. Fanning, M.D., Ph.D.
Associate Director for Medical Affairs
Office of Generic Drugs

MEDICAL OFFICER SUMMARY
January 27, 2000

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Drug Product: Ketoconazole, 2% Cream
Sponsor: TEVA Pharmaceuticals

Review of statistical report

The statistical report concludes that: "Both active treatment arms appear to be effective when compared to the placebo arm. The submitted data support the claim that TEVA's Ketoconazole and the reference drug, Nizoral, are equivalent."

Conclusion

The submitted study supports the claim that the test drug, TEVA's Ketoconazole is bioequivalent to the reference drug, Nizoral.

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