CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76005

MEDICAL REVIEW

MEDICAL OFFICER REVIEW
December 11, 2001

ANDA 76-005
Drug Product: Econazole Nitrate Cream, 1%
Sponsor: Taro Pharmaceuticals, Inc.
Reference Listed Drug: Spectazole ® Cream, 2%, Ortho-McNeil Pharmaceuticals

The statistical consultation was reviewed. The therapeutic cure rate was recalculated based on the mycological and clinical cure rate at week 6. Using this definition, the therapeutic cure rate at week 6 for the Evaluable population was 63% for Taro's product, 50.6% for Ortho's product and 21.3 % for the placebo (vehicle). The 90% confidence interval did not meet the bioequivalence criteria. Although the clinical cure rate for week 6 and week 4 passes bioequivalence criteria, the mycological cure rate for both endpoints fail bioequivalence criteria. In addition, neither the Ortho nor the Taro products are better than placebo for clinical cure rate at week 6.

Conclusion

This study fails to demonstrate bioequivalence of Taro Pharmaceuticals, Inc.'s Econazole Nitrate Cream, 1% with the reference listed drug, Spectazole ® Cream, 2%, Ortho-McNeil Pharmaceuticals.

/S/

Mary M. Fanning, MD, PhD
Associate Director for Medical Affairs
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ANDA 76-005
Comments for the sponsor
5 January, 2002

1. The therapeutic cure should be based on mycological and clinical cure rate at week 6, and not on a mycological cure rate based on outcomes at week 4 and 6.

2. A modified intent-to-treat (MITT) population, omitting patients lost to follow-up after visit 1, was used for the comparison of the active treatment groups with the placebo arm.

3. The Evaluable population was used for the comparison of test and reference groups in the determination of bioequivalence. Patients who did not return after visit 2 or were outside the visit window of +/- 3 days for visit 3 were not included in this population.

4. The comparison between the active treatment arms and the vehicle (placebo) arm was done using the MITT population. The 90% confidence interval method is not the correct method for this analysis.

5. The 90% confidence interval for the difference in therapeutic cure rate between the test and reference drug did not meet the bioequivalence criteria.

/S/
Mary M. Fanning, MD, PhD

MEDICAL OFFICER REVIEW
June 15, 2001

ANDA 76-005
Drug Product: Econazole Nitrate Cream, 1%
Sponsor: Taro Pharmaceuticals, Inc.
Reference Listed Drug: Spectazole ® Cream, 2%, Ortho-McNeil Pharmaceuticals

Title: A Comparison of the Safety and Efficacy of Two Econazole Nitrate 1% Cream Formulations in the Treatment of Patients with Clinically Symptomatic and Mycologically Confirmed Tinea Pedis.

Protocol Number: ECZ 9902

Enrollment Period: January 17, 2000 to May 30, 2000

Objectives

The objective of the present study was to establish the bioequivalence of econazole nitrate cream 1% manufactured by Taro Pharmaceuticals Inc. (Taro) to econazole nitrate cream 1% cream manufactured by Ortho Pharmaceutical Corp. (Spectazole® 1%) (Ortho) US; and to show superiority of the Taro formulation to placebo in the treatment of tinea pedis.

The secondary objective of the study was to compare the adverse event profile of the creams to establish that the creams had no unanticipated adverse effects.

Study Design

This was a double-blind, randomized, parallel group, placebo-controlled study comparing Taro's econazole cream to Ortho's Spectazole ® in patients with clinical signs and symptoms and mycologically proven tinea pedis. Enrolled patients were randomized to receive one of 3 treatments:

1. Spectazole ® 1% (Ortho Pharmaceuticals) Lot# 29G801
2. Taro Econazole Nitrate 1% Cream Lot # S123-51820
3. Taro Vehicle (Placebo) Lot # S123-51868

Patient Selection

Patients had to meet the following inclusion and exclusion criteria:

Inclusion Criteria

1. All patients had to be at least 18 years of age.
2. Only men or non-pregnant females.
3. Clinical evidence of tinea pedis with some degree of erythema, pruritus, and scaling.
4. Subsequently, a culture positive for *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum* must be demonstrated for the patient to be considered eligible.
5. Signed informed consent.

Exclusion Criteria

1. Pregnancy or nursing.
2. Bacterial or viral skin infections in the study area other than tinea pedis.
3. Poorly controlled diabetes mellitus.
4. History of allergy or sensitivity to econazole or related compounds.
5. Clinically significant current abnormal liver function studies (LFT's were assumed to be normal if patient claimed to be in good health).
6. Evidence of subungual infection.
7. Severe thick (hyperkeratotic) scaly lesions. (These lesions frequently require more than 4 weeks of therapy).
8. Current use, or use within the past 30 days, of oral antibiotics or oral or topical antifungal preparations (to the study area).
9. Use of any topical (to the study area) or systemic corticosteroids within the past 30 days.

Reasons for Discontinuation

Patients may be discontinued from the study for any of the following:

1. Patient's decision to or stated intention to leave the study for any reason.
2. Development of an intercurrent condition or complication which would affect the safety of the patient or the validity of evaluation of the patient's clinical state to an extent considered significant by the investigator.
3. Use of any oral antibiotic, oral antifungal agent, or any topical (to the study area) antibiotic or topical antifungal agent or use of any over-the-counter athlete's foot remedies, anti-pruritus products, or any other topical treatments on the study are for the 6 weeks of the study.
4. Failure or inability to comply with the protocol.
5. Patients will not be permitted to take any oral antibiotics or antifungal agents, or apply any other medications to the affected areas for the six weeks of the study.

Patients were enrolled if they met these inclusion/exclusion criteria and had skin scrapings taken from an area of active lesions for 10% KOH wet mount and fungal

culture. Those subjects whose cultures were negative after 4 weeks of incubation were discontinued from participation in the study and excluded from the data analyses.

Study Sites

The principal investigator was Dr. Howard Yanofsky. He recruited subjects through his offices at the University of Montreal, and McGill University, and his private office in Montreal, Quebec.

Study Conduct

Enrollment Visit: At the enrollment visit, subjects were evaluated for eligibility. Patients were enrolled if they met the inclusion and exclusion criteria, provided informed consent, and had a clinical evaluation of signs and symptoms, and skin scrapings taken from an area of active lesions for 10% KOH wet mount and fungal culture. Signs and symptoms include itching, burning, erythema, scaling, fissuring, and bulla formation. The investigator, office staff, and study subjects were blinded to the treatment assignment. Patients were instructed to apply the cream to the clean, dry study foot twice a day for four weeks.

Visit 2 (Week 4, End of Treatment):
Visit 3 (Week 6, 2 weeks off treatment): Clinical signs and symptoms were recorded and specimens collected for 10% KOH wet mount and fungal culture. Occurrence of adverse events and use of concomitant medications were recorded. Used and unused medications were returned at Visit 2.

Efficacy Evaluations

Symptoms were evaluated using a scoring system. The patients rated pruritus and burning on this 5-point scale:

0	None
1	Mild
2	Moderate
3	Moderately severe
4	Severe or extensive

The investigator or study personnel rated erythema, scaling, fissuring and bulla formation on this 5-point scale:

0	None
1	Mild
2	Moderate
3	Moderate/Severe
4	Severe

The total sum of scores was calculated by adding the scores on the individual symptoms. Scrapings of the skin lesions were sent for fungal culture and 10% KOH wet mount.

Analysis

Definitions

The testing of efficacy was primarily based on the mycological cure rate and the clinical cure rate at the 4 and 6-week visits.

Mycological Cure – Culture negative at weeks 4 and 6 and KOH smear negative at weeks 4 and 6.

Clinical Cure – The subject had a total score of 2 or less and a severity score of no more than 1 for any of the 6 clinical parameters at the 6 week visit.

Therapeutic Cure – Both a clinical and a mycological cure: KOH (if available) and culture negative at week 6 as well as clinical cure at week 6.

Treatment Failure – Inadequate clinical or mycological response and/or treatment-related adverse events that required discontinuation from the study. In addition, any patient who failed to return for one of the follow-up visits, and was a mycological or clinical failure for the other follow-up visit was included as a treatment failure.

> *Medical Officer Note: The therapeutic cure should be based on mycological and clinical cure rate at week 6, and not on a mycological cure rate based on outcomes at week 4 and 6.*

Populations

The sponsor only defined one population, the Evaluable population, and used this for both the bioequivalence and efficacy analyses.

Evaluable patients were those who completed the study. The protocol states that "If in the Investigator's view the disease has become worse at or before the 4 week visit, the patient may be declared a treatment failure." In the analysis, this patient was to be considered a mycologic and treatment failure for the remaining visit(s), although they were dropped from the study. Patients who did not complete the study due to a drug related adverse event, those who were dropped due to protocol violations, and those who were lost to follow up or did not complete all visits were to be categorized as treatment failures.

Sample size

The sample size was chosen to demonstrate bioequivalence of Taro's product versus the reference product with a power of 0.80, delta of 0.20, and alpha of 0.10, based on an

estimated cure rate of 70%. Seventy-five subjects were needed per arm to assess bioequivalence.

Statistical Analyses

All statistical tests were performed using the SAS ® statistical package (Version 8). All tests were performed as two-tailed tests and effects were considered to be statistically significant if $p<0.05$. The efficacy endpoints were compared among the 2 treatment and the placebo groups using the Chi square and Fisher's exact test. Ninety-percent confidence intervals were calculated using Blackwelder's method for the assessment of bioequivalence. The association between investigator and cure was tested by the Cochran-Mantel-Haenszel (CMH) statistics.

RESULTS

Cohort

Five hundred fifty-three (453) men and women with signs and symptoms of tinea pedis were enrolled and randomized to one of the three study arms (2.6 male to female ratio). One- hundred fifty-two (152) were treated with Spectazole US, 151 received Taro's econazole, and 132 received the vehicle (placebo). Of these, 199 had a negative fungal culture and 2 were ineligible because of protocol violations. Thus, 252 subjects were eligible for evaluation – 84 Spectazole US, 81 Taro, and 87 Placebo.

Medical Officer Note: This should be considered the Intent-to-Treat population. The modified intent-to-treat (MITT) population, omitting patients lost to follow-up should be used for the comparison of the active treatment groups with the placebo arm (ITT).

Of these 252 eligible subjects, 5 eligible patients did not return for follow-up. Thus, the evaluable population had 247 patients – 81 Spectazole US, 81 Taro, and 85 Placebo. The patient populations were evenly divided among the treatment arms (Table I).

Medical Officer Note: This would be considered the Per Protocol or Evaluable population to be used for the comparison of test and reference groups in the determination of bioequivalence. Table I has been constructed based on the Medical Officer's assessment of the relevant populations, to include a Modified Intent-to-Treat (MITT) and an Evaluable population. The sponsor identified 5 patients who did not return for follow-up and were therefore excluded from their evaluable population. On review of the primary data, these patients fit the following criteria, #297 did not return after visit 2, and #300, 335, 482, and 707 did not return after visit 1. In fact, there were 8 patients who did not complete all the study visits. Patient #482 had visit 2 but no visit 3 data, patients #427, 429, and 778 did not return for visit 2 but had visit 3 data, and as noted by the sponsor, patients #300, 335, and 707 had only visit 1 data.

There were 17 patients who had protocol deviations. They did not meet the Inclusion Criteria of "at least moderately severe scaling". However, these patients had high symptom scores for other signs and symptoms and were therefore included as evaluable patients.

Table I
Patient populations and exclusions per treatment arm (per Medical Officer)

	Spectazole	**Taro**	**Placebo**	**Total**
ENROLLED	152	151	150	453
Baseline culture negative	67	69	63	199
Protocol violation*	1	1	0	2
Lost to Follow-up	0	1	2	3
ELIGIBLE (MITT)	84	80	85	249
No visit 2 data	1	1	1	3
Did not return or dropout after visit 2	0	2	0	2
EVALUABLE	83	77	84	244

- Did not meet eligibility criteria – the specific criteria were not specified in the study report or the patient data provided.

Medical Officer Note: The sponsor should be asked to provide the case report forms for the two patients (#159 and # 763) who were classified as protocol violations since the report does not specify the basis for this determination.

The MITT population to be used for the efficacy analysis should include the following four patients, #297, 427, 429, and 778.

The sponsor did not define the visit window. A visit window of + or – 3 days is usually used for this type of study. When this visit window is applied, the following 9 patients were outside the visit windows:

Visit 2	Visit 3
#293	#407
#432	#421
#444	#722
#477	#744
#722	#752

Medical Officer Note: The patients outside the visit 3 window should be excluded from the Evaluable population.

Demographics

Overall, there were 195 (77%) males and 57 (23%) females in the total cohort. In addition, 83% of the subjects were white, 9% black, 7% Hispanic and 1% Asian. The sex and race of subjects was comparably distributed among the three treatment arms. Mean age for the group was 37.1 with a range of 19-83. Although the 28 patients at Center 2 were significantly younger than at the other centers with a mean age of 23.9 compared to 38.4 and 39.1 years, age was comparable in all treatment arms and in comparing males and females.

Baseline total symptom scores are shown in Table II below. They were comparable among the four treatment arms. The main symptoms experienced were scaling and erythema with itching, fissuring, and burning reported a little less frequently. Bullae were the least frequent with a mean score ranging from 0 to 0.01 in the four groups. The highest possible score was 24. The individual symptom scores were compared at each center, and according to sex, and race. There were statistically significant differences across study centers. Center 1 and 4 had higher scores than centers 2 and 3 in the severity of baseline scaling, erythema, itching, burning, and total score.

Table II
Baseline Sign/Symptom Scores

Sign/Symptom	Spectazole US	Taro	Placebo
	Mean (SE)	Mean (SE)	Mean (SE)
Scaling	2.61 (0.08)	2.59 (0.09)	2.61 (0.09)
Erythema	2.10 (0.05)	2.21 (0.07)	2.11 (0.07)
Fissuring	1.42 (0.06)	1.58 (0.08)	1.57 (0.07)
Bullae	0.05 (0.02)	0.09 (0.04)	0.09 (0.05)
Itching	2.82 (0.11)	2.93 (0.10)	2.80 (0.11)
Burning	2.83 (0.11)	2.74 (0.13)	2.66 (0.13)
Mean Total	11.82 (0.30)	12.10 (0.30)	11.85 (0.27)

There were no significant differences in the mean baseline symptom scores across the treatment groups or by race or gender.

Forty-one percent of the patients had chronic moccasin type infection, 54% had acute interdigital infection and 6% had chronic interdigital Tinea pedis.

The majority of subjects grew *Trichophyton rubrum* (84%) in their fungal culture. The others were positive for *Trichophyton mentagrophytes* (10%) and the remainder grew *Epidermophyton floccosum* (6%). There were no differences among the treatment groups in the distribution of organisms identified.

The sponsor did not provided any information on medication at the baseline visit or during the study or on the evaluation of patient compliance.

Medical Officer Note: The sponsor should be asked to provide information on medication use during the study as well as data collected on compliance.

Efficacy/Bioequivalence

The primary endpoint was Therapeutic Cure: KOH (if available) and culture negative at visit 2 (Week 4) and visit 3 (Week 6) as well as clinical cure at visit 3 (Week 6). The sponsor did all the analyses on the Evaluable population (Completed subjects). The sponsor's analysis of the mycological, clinical and therapeutic cure rates for the 3 treatment arms, using the definitions provided earlier in this review, are shown in Table III. The 90% confidence intervals calculated by the sponsor using the Blackwelder method are shown in Table III.

Medical Officer Note: The comparison between the active treatment arms and the vehicle (placebo) arm should be done using the Intent-to-Treat population. The 90% confidence interval method is not the correct method for this analysis.

Table III
Mycological, Clinical, and Therapeutic Cure Rates at Week 6, Evaluable population (per Sponsor)

Treatment	Number	Mycological Cure	Clinical Cure	Therapeutic Cure
Spectazole US	81	67.5%	70.4%	46.9%
Taro	81	67.5%	72.8%	53.1%
Placebo	85	25.9%	48.2%	20%
90% Confidence Intervals				
Spectazole vs. Taro		-12.2, 12.2	-14.1, 9.2	-19.1, 6.7
Spectazole vs. Placebo		29.2, 52.4	9.9, 34.3	15.3, 38.5
Taro vs. Placebo		52.4, 52.4	12.5, 36.7	21.5, 44.7

Table IV shows the 90% confidence intervals for the cure rates provided by the sponsor calculated using a continuity correction. This analysis of bioequivalence is different than the one conducted by the sponsor. Using this analysis for the primary endpoint (therapeutic cure), Spectazole ® and the Taro product are not bioequivalent as assessed by the primary endpoint of the therapeutic cure.

Table IV
90% Confidence Intervals Using the Continuity Correction Factor, Evaluable Population

Comparison	**Mycological Cure**	**Clinical Cure**	**Therapeutic Cure**
Spectazole® versus Taro	-13.3, 13.3	-16.51, 9.10	-20.31, 7.9

Safety

No adverse events were reported during the study.

Conclusion

The study conduct is acceptable. However, the appropriate statistical analysis to document efficacy of the active treatments compared to placebo needs to be done. In addition, the mycological, clinical, and therapeutic cure rates need to be recalculated with the following changes:

1. The MITT population to be used for the efficacy analysis should include the following four patients, #297, 427, 429, and 778.

2. The patients outside the visit 3 window, #407, 421, 722, 744, and 752, should be excluded from the Evaluable population.

3. The therapeutic cure should be based on mycological and clinical cure rate at week 6, and not on a mycological cure rate based on outcomes at week 4 and week 6.

Recommendation

This study should be sent for a statistical consult. The sponsor should be asked to provide the following information:

1. The sponsor should be asked to provide the case report forms for the two patients (#159 and # 763) who were classified as protocol violations since the report does not specify the basis for this determination.

2. The sponsor should be asked to provide information on medication use during the study as well as data collected on compliance.

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