

Clinical Review Section

Table IV: Primary Efficacy Analysis: Therapeutic Cure¹ Rate at Visit 3 (per sponsor)

Parameter	TARO	RLD	90% C.I. for Bioequivalence of Taro's product to Lamisil ^{AT} Cream 1% (OTC)		
Per-Protocol Patients					
Visit 3	(N=191)	(N=195)			
Therapeutic Cure	133 (70%)	141 (72%)	(-10.8%, 5.4%)		
Clinical Cure	142 (74%)	155 (79%)	(-12.7%, 2.4%)		
Mycological Cure	177 (93%)	176 (90%)	(-2.8%, 7.6%)		
Intent-to-Treat Patients					
	TARO	RLD	Vehicle	P-Value (2-sided cc Z-test)	
Visit 3	(N=199)	(N=199)	(N=102)	T vs. Vehicle	Ref vs. Vehicle
Therapeutic Cure	136 (68%)	142 (71%)	3 (3%)	<0.0001	<0.0001
Clinical Cure	145 (73%)	156 (78%)	41 (40%)	<0.0001	<0.0001
Mycological Cure	181 (91%)	177 (89%)	8 (8%)	<0.0001	<0.0001

¹ Mycological cure defined as culture and KOH negative at the 6-week visit.

Clinical cure defined as erythema score ≤ 2 and sum of all other symptom scores < 2 at the 6-week visit.

Therapeutic cure defined as having both a clinical and mycological cure.

Patients missing the 6-week visit designated as mycological, clinical, and therapeutic failures for the ITT population analysis only.

Reviewer's Comments:

- The sponsor included patient #462 (reference) who used prohibited medication in the per protocol analysis. This patient received Lamisil for treatment of fungus infection in the groin area 1 week prior to the study treatment day. Although Lamisil use is considered a protocol violation, since it was not applied to the study site, this reviewer agrees with the sponsor's decision to include this patient in the per protocol analysis.*
- No patient discontinued the study due to lack of treatment effect.*

D. Bioequivalence Conclusion

Based on the FDA statistical analyses, the study demonstrates that the 90% CI of the difference in therapeutic cure rates between the test and the reference products at visit 3 (Week 6) is (-0.108, 0.054), which is within the bioequivalence limits of (-.20, +.20). A patient was considered a clinical cure by the sponsor if erythema score is ≤ 2 and sum of all other symptom scores are < 2 at the 6-week visit. A patient was considered a mycological cure if he or she had negative KOH and negative fungal culture at the 6-week visit.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

This study showed no significant difference between the generic and reference products with regard to the adverse events reported.

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B. Description of Adverse Events

A total of 164 adverse events (66 in the test, 58 in the reference, and 40 in the vehicle group) occurred in 535 randomized patients. Seventy (70) of the 164 adverse events were skin related adverse events (25 test, 24 reference, and 21 vehicle). Fifty-three (53) of the 164 adverse events [19(8.9%) test, 19(8.9%) reference, and 15 (10.3%) vehicle] were thought to be treatment related adverse events by the investigator. Burning (3.7% test, 3.3% reference, and 7.5% vehicle) at the application site was the most frequent skin related adverse event reported in all treatment groups.

No death occurred in the study. Two patients reported adverse events that were considered serious by the investigator. Patient 469 (test) was hospitalized and underwent surgery to repair a fracture of the femur caused by a sports injury. Patient 362 (vehicle) was hospitalized for a severe asthma attack. None of these events were considered study treatment related.

The sponsor's summary of frequency of adverse events is listed below.

Summary of Adverse Events (per sponsor)

Treatment Group:									
Test (N=214)									
	Mild	Mild	Moderate	Moderate	Severe	Severe	Total	Total	Total
Event	Related	Not related	Related	Not related	Related	Not related	Related	Not related	
Allergy		1 (0.5%)						1	1
Arthritis		1 (0.5%)						1	1
Back pain		2 (0.9%)						2	2
Burning	8 (3.7%)	1 (0.5%)					8	1	9
Cold		8 (3.7%)		2 (0.9%)				10	10
Cold sores		1 (0.5%)						1	1
Fatigue		1 (0.5%)						1	1
Fissuring		1 (0.5%)						1	1
Fracture						1 (0.5%)		1	1
Headache	1 (0.5%)	8 (3.7%)					1	8	9
Injury		3 (1.4%)		2 (0.9%)				5	5
Insomnia		1 (0.5%)						1	1
Irritation	2 (0.9%)	1 (0.5%)					2	1	3
Itching	3 (1.4%)	3 (1.4%)					3	3	6
Muscle pain		1 (0.5%)						1	1
Numbness		1 (0.5%)						1	1
Renal colic				1 (0.5%)				1	1
Sore cheek		1 (0.5%)						1	1
Sore throat		1 (0.5%)						1	1
Surgery						1 (0.5%)		1	1
Swelling	2 (0.9%)						2		2
Swollen lymph node	1 (0.5%)						1		1
Tingling	2 (0.9%)						2		2
Toothache		2 (0.9%)		1 (0.5%)				3	3
Vaginal infection				1 (0.5%)				1	1
Total	19 (8.9%)	38 (17.8%)		7 (3.3%)		2 (0.9%)	19	47	66

(%) denotes the percent of total subjects within treatment groups

Clinical Review Section

Treatment Group:									
Reference (N=214)									
Event	Mild	Mild	Moderate	Moderate	Severe	Severe	Total	Total	Total
	Related	Not related	Related	Not related	Related	Not related	Related	Not related	
Bleeding		1 (0.5%)						1	1
Burning	7 (3.3%)						7		7
Cold		7 (3.3%)		1 (0.5%)				8	8
Ear infection				1 (0.5%)				1	1
Fissuring	2 (0.9%)	2 (0.9%)					2	2	4
Fracture		1 (0.5%)						1	1
Gastroenteritis		1 (0.5%)						1	1
Headache		14 (6.5%)		2 (0.9%)				16	16
Irritable bowel syndrome				1 (0.5%)				1	1
Irritation	4 (1.9%)						4		4
Itching	2 (0.9%)						2		2
Muscle pain		3 (1.4%)						3	3
Rash		1 (0.5%)						1	1
Surgery		1 (0.5%)						1	1
Swelling	1 (0.5%)						1		1
Tingling	3 (1.4%)	1 (0.5%)					3	1	4
Tonsillitis		1 (0.5%)						1	1
Urinary tract infection		1 (0.5%)						1	1
Total	19 (8.9%)	34 (15.9%)		5 (2.3%)			19	39	58
(%) denotes the percent of total subjects within treatment groups									
Treatment Group:									
Vehicle (N=107)									
Event	Mild	Mild	Moderate	Moderate	Severe	Severe	Total	Total	Total
	Related	Not related	Related	Not related	Related	Not related	Related	Not related	
Arthritis		1 (0.9%)						1	1
Asthma						1 (0.9%)		1	1
Burning	4 (3.7%)	1 (0.9%)	4 (3.7%)				8	1	9
Cold		7 (6.5%)						7	7
Desquamation		2 (1.9%)						2	2
Fracture				1 (0.9%)				1	1
Headache		4 (3.7%)						4	4
Injury				1 (0.9%)				1	1
Irritation	2 (1.9%)	1 (0.9%)					2	1	3
Itching	1 (0.9%)	1 (0.9%)					1	1	2
Menstrual pain		1 (0.9%)						1	1
Muscle pain		1 (0.9%)						1	1
Sore throat		1 (0.9%)						1	1
Tendonitis				1 (0.9%)				1	1
Tingling	4 (3.7%)	1 (0.9%)					4	1	5
Total	11 (10.3%)	21 (19.6%)	4 (3.7%)	3 (2.8%)		1 (0.9%)	15	25	40
(%) denotes the percent of total subjects within treatment groups									

Reviewer's Comments: The reported frequency of skin related adverse events in this study is comparable between the test and reference groups. Although the approved labeling notes a smaller percentage of patients reported burning/tingling (0.9%) with use of the reference product than the proportion noted in this study, the medical officer's review of the original NDA 20-980 (review dated 1/29/99) noted that in 550 patients treated with terbinafine HCl cream 1% in 9 clinical studies, up to 29.8% of patients reported burning.

Clinical Review Section

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Review of the Division of Scientific Investigation (DSI) Report

Dr. Yanofsky's office was previously inspected by the DSI for ANDA 75-883 (Ammonium Lactate Cream, 12%). Based on the final report issued on February 26, 2003, a Form FDA-483 was issued because the investigator did not comply with the requirement for retention of study drugs as per 21 CFR 320.38 and 320.63 at this site. Other than retention sample issue, the study was acceptable for the review.

A subsequent inspection (1/20/04) for 75-953 (terconazole vaginal cream) did not find any deficiency related to retention samples, and no Form FDA-483 was issued although the sponsor had not provided a sealed copy of the randomization code to the site.

Reviewer's Comment: Based on acceptable previous inspection history of Dr. Yanofsky's clinical site, no DSI inspection was requested for this study.

B. Review of the FDA Statistical Report (12/21/05)

The conclusion of the FDA statistical analysis confirms the bioequivalence of the test and the reference products. The 90% CI of the difference in therapeutic cure rates for the per protocol population at the primary endpoint (Visit 3, Week 6) is (-0.108, 0.054), which is within the bioequivalence limits of (-.20 and +.20). Both the test and the reference products showed superiority over the placebo group at Visit 3.

Based on this reviewer's comments above, nine patients (27, 407, 638, 674, 693, 776, 855, 912, and 955) were excluded from the sponsor's ITT population. These patients did not return after visit 1 (enrollment visit) and/or missed visit 3.

The FDA statistician provided the summary of the equivalence test for the per protocol population and efficacy analyses for the ITT population as follows:

Primary Endpoint: Therapeutic cure rates at visit 3 (Week 6)

Population	Test* % successes (No. of successes /total)	Reference* % successes (No. of successes /total)	Placebo* % successes (No. of successes /total)	p-value# for Test vs. Placebo	p-value# for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
FITT	69.7 (136/195)	72.5 (142/196)	3.0 (3/100)	<0.001	<0.001		
PP	69.6 (133/191)	72.3 (141/195)	3.0 (3/99)			-10.8, 5.4	Yes

*: The rate of success equals the number of successes divided by the total number, then multiplied by 100.

#: The p-values were from Fisher's exact test (2-sided).

FITT: All subjects randomized to treatment, treated, and who had an assessment at visit 3/week 6 (follow-up visit).

Clinical Review Section

Efficacy and equivalence analyses for secondary endpoints

Population /endpoint	Test % successes (No. of successes /total)	Reference % successes (No. of successes /total)	Placebo % successes (No. of successes /total)	p-value for Test vs. Placebo	p-value for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
FITT							
Mycological response	92.8 (181/195)	90.3 (177/196)	8.0 (8/100)	<0.001	<0.001		
Clinical response	74.4 (145/195)	79.6 (156/196)	41.0 (41/100)	<0.001	<0.001		
PP							
Mycological response	92.7 (177/191)	90.3 (176/195)	8.1 (8/99)	<0.001	<0.001	-2.8, 7.6	Yes
Clinical response	74.4 (142/191)	79.5 (155/195)	40.4 (40/99)	<0.001	<0.001	-12.7, 2.4	Yes

Reviewer's Comment: *The conclusion of the FDA statistical analysis confirms the bioequivalence of the test and the reference products.*

VII. Formulation

Taro's formulation

Component	Taro formulation Quantity per unit (mg/g); 1% strength, 10 mg/g	RLD formulation* Per gram
Terbinafine hydrochloride	10	10.0
Purified water, USP	(b) (4)	(b) (4)
Polysorbate 60, NF		
Cetyl alcohol, NF		
Stearyl alcohol, NF		
Cetyl palmitate, NF		
Isopropyl myristate, NF		
Sorbitan monostearate, NF		
Sodium hydroxide, NF		
Benzyl alcohol, NF		
Total weight/volume	1000 mg	1000 mg

*Per medical officer's review of the 1% prescription Lamisil® Cream, NDA 20-192 (9/25/92). The RLD, OTC formulation (Lamisil^{AT} 1% Cream, NDA 20-980) is identical to the 1% prescription cream.

Reviewer's Comment: *The test product is qualitatively the same but quantitatively different from the reference product. It contains significantly lower amounts of (b) (4). The results of this study suggest that these quantitative differences in inactive ingredients will not result in any differences in safety or efficacy of the product.*

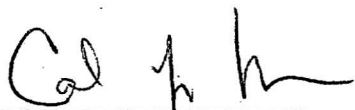
VIII. Conclusion and Recommendation

A. Conclusion

The data presented in this ANDA 77-511 demonstrate that Taro Pharmaceuticals Inc.'s Terbinafine Hydrochloride Cream, 1%, is bioequivalent to the reference listed drug, Lamisil^{AT} Cream, 1%. The FDA statistical review confirms that the 90% CI of the difference in therapeutic cure rates between the test and reference products at the 5 weeks follow-up visit (Visit 3, Week 6) is within the bioequivalence limits of (-.20,+.20). The test and reference products also demonstrate superiority over Placebo arm at Visit 3.

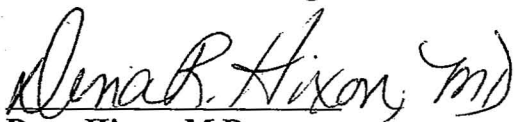
B. Recommendations to be conveyed to Sponsor

The data submitted to ANDA 77-511, using the primary endpoint of therapeutic cure rate at the 5 weeks follow-up visit (Visit 3, Week 6), are adequate to demonstrate bioequivalence of Taro Pharmaceuticals USA, Inc.'s Terbinafine Hydrochloride Cream, 1%, with the reference listed drug, Novartis' Lamisil^{AT} 1% Cream.



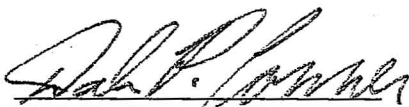
Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

12/28/05
Date



Dena Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

1/03/06
Date



Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

1/6/06
Date

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:77-511

APPLICANT: Taro Pharmaceuticals USA, Inc.

DRUG PRODUCT: Terbinafine Hydrochloride Cream, 1%

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 77-511, using the primary endpoint of therapeutic cure rate at the 5 weeks follow-up visit (Visit 3, Week 6), are adequate to demonstrate bioequivalence of Taro Pharmaceuticals USA, Inc.'s Terbinafine Hydrochloride Cream, 1%, with the reference listed drug, Novartis' Lamisil^{AT} 1% Cream.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-511

ANDA DUPLICATE

DIVISION FILE

HFD-651/ Bio Drug File

HFD-600/ C.Kim

HGD-600/ D. Hixon

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Endorsements: (Final with Dates)

HFD-600/C. Kim *CW 11/8/05*

HFD-600/D. Hixon *DRH 1/03/06*

HFD-650/D. Conner *DM 1/6/06*

BIOEQUIVALENCY - ACCEPTABLE

submission date:

December 30, 2004

1. Bioequivalence Study (STU); 12/30/04
(new study)

Strengths: 1%

Outcome: AC

Please note: This review should close the BCE and BST assignments.

Outcome Decisions: AC - Acceptable
WC - Without charge
IC - Incomplete
UC - Unacceptable

OFFICE OF GENERIC DRUGS

DIVISION OF BIOEQUIVALENCE

ANDA #: 77-511

SPONSOR : Taro Pharmaceuticals USA, Inc.

DRUG AND DOSAGE FORM : Terbinafine Hydrochloride Cream, 1%

STRENGTH(S) : 1%

TYPES OF STUDIES : Clinical Endpoints

CLINICAL STUDY SITE(S) : Dr. Yanofsky office (Montreal, Quebec)

STUDY SUMMARY: Study is acceptable.

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection report: N/A	Inspection results: N/A
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

PRIMARY REVIEWER : Carol Y. Kim, Pharm. D.

INITIAL : Cal Y Kim DATE : 12/28/05

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS: Dena R. Hixon, M.D.

INITIAL : DRH DATE : 1/3/06

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL : APC DATE : 1/6/06

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 77-511

STATISTICAL REVIEWS

ANDA 77-511

Drug Product: Terbinafine hydrochloride cream, 1%

Sponsor: Taro Pharmaceuticals

Reference Listed Drug: Lamisil® Cream (terbinafine hydrochloride), 1%, Novartis

Submission date: 12/30/2004

V:/firmsnz/taro/ltrs&rev/77511st.doc

Reviewer: Huaixiang Li, Ph.D., QMRS/OB/CDER

Requestor: Dena Hixon, MD, Carol Kim, Pharm.D., OGD/CDER, 10/21/2005

Objectives of the study

The primary objective of the study was to establish the bioequivalence of the test product, Taro Pharmaceuticals, Terbinafine Hydrochloride Cream, and the reference product, Novartis Pharmaceutical Corporation, Lamisil® Cream, and to show superiority of the two active treatments to the placebo, a cream vehicle, in the treatment of tinea pedis.

Remarks

The sponsor submitted SAS datasets and programs to the Electronic Document Room (EDR), CDER on December 30, 2004. The statistical analyses used information from one dataset: 'data.xpt'.

The following adjustment to this submitted dataset was made in accordance with recommendations of the FDA medical and statistical reviewers¹.

Exclusion from the FDA's Intent-to-treat population (FITT)

Nine patients, 27, 674, 912, and 955 in the test treatment group, 407, 693, and 776 in the reference treatment group, 638 and 855 in the placebo group, did not return after visit 1 (enrollment visit) and/or missed visit 3². These patients were originally excluded from the sponsor's PP population, but not the Sponsor's ITT population.

Study Design

This was a 3 arm parallel double-blind study in patients with signs and symptoms of tinea pedis. The three creams were the test product, Taro Pharmaceuticals, Terbinafine Hydrochloride Cream, the reference product, Novartis Pharmaceutical Corporation, Lamisil® Cream, and the placebo, a cream vehicle.

535 patients were enrolled and randomly assigned to three treatment groups in a 2:2:1 ratio (test:reference:placebo) in the study.

¹ Please see the details on page 4 in this report and the FDA medical reviewer's report.

² This study had three visits, visit 1 (enrollment), visit 2 (end of treatment), and visit 3 (follow-up). Patients returned study medicine and diary, were questioned about AE, etc. with no measurement for signs/symptoms and test for KOH/culture at visit 2. The efficacy and equivalence analyses could not be carried out when the patient(s) missed visit 3.

At the enrollment visit (visit 1), patients with clinical signs and symptoms of tinea pedis had a skin scraping taken from an area of active lesions for KOH mount and fungal culture. Signs and symptoms - erythema, scaling, fissuring, maceration, vesiculation, exudation, pruritus/itching, and burning - were measured by using a score (0-3, none to severe). Eligible subjects, who had a positive KOH result and met the eligibility criteria, were instructed to apply the cream to the clean, dry study foot twice a day for 7 days.

At visit 2/week 1 (end of treatment visit), patients were instructed to return the study medication and diary, were questioned about possible adverse events and compliance with the protocol, and repeated urine pregnancy test if of childbearing potential.

At visit 3/week 6 (follow-up visit), the mycological evaluations (both KOH and fungal culture test) were performed and the signs/symptoms were measured.

Outcome Variables at Visit 3

The sponsor provided the mycological cure rate, clinical cure rate, and therapeutic cure rate at visit 3.

The FDA medical reviewer requested analysis of the Primary endpoint – Therapeutic cure rate, and the secondary endpoints – Mycological cure rate and clinical cure rate at visit 3/week 6 (Follow-up visit).

Definitions:

Mycological cure: negative KOH and culture.

Clinical cure: an erythema score ≤ 2 with the sum of all other signs/symptoms scores < 2 .

Therapeutic cure: both a mycological cure and a clinical cure.

Statistical Analysis Methods

Efficacy Analysis

All treatment arms should be similar for signs/symptoms scores at the enrollment visit.

The efficacy analyses for the therapeutic cure rate were carried out by using Fisher's exact test (two-sided) for each active treatment versus placebo with a two-sided significance level of $\alpha=0.05$.

The active treatments should have been more distinguishable from placebo as the study progressed.

Equivalence Analysis

Based on the usual method used in the Office of Generic Drugs (OGD) for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within $-.20$ to $.20$ in order to establish equivalence.

The compound hypothesis to be tested is:

$$H_0: \begin{array}{l} p_T - p_R < -.20 \\ \text{or} \quad p_T - p_R > .20 \end{array}$$

versus

$$H_A: \quad -.20 \leq p_T - p_R \leq .20$$

where p_T = cure rate of test treatment p_R = cure rate of reference treatment

Let n_T = sample size of test treatment n_R = sample size of reference treatment

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

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

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

Analysis Populations

Two analysis populations were used in this statistical reviewer's report:

FDA's Intent-to-treat population (FITT) – All subjects randomized to treatment, treated, and who had an assessment at visit 3/week 6 (follow-up visit).

Per protocol population (PP) – All subjects in the FITT population who were evaluable for the analyses based on the protocol and FDA medical and statistical reviewer's best judgment. The sponsor's PP population met the requirement in this study.

According to the FDA medical reviewers, the determination of clinical equivalence of the two active treatments was to be assessed using the sponsor's per protocol population (PP), while the superiority comparison of the two active treatments to placebo was to be assessed using the FDA's intent-to-treat population (FITT).

Statistical Analysis Results

535 patients were enrolled. The FITT population included 491 patients and the PP population included 485 patients.

This table shows the number of patients in each population per treatment arm[&]

	Terbinafine	Lamisil®	Placebo	Total
Enrollment	214	214	107	535
<i>Negative baseline KOH</i>	<i>1</i>	<i>0</i>	<i>1</i>	<i>2</i>
<i>Negative baseline culture</i>	<i>14</i>	<i>15</i>	<i>4</i>	<i>33</i>
Sponsor's ITT population	199	199	102	500
Exclusion from the FITT population				
Did not return after visit 1 (enrollment visit)*	4	3	2	9
FDA's FITT population	195	196	100	491
Exclusion from the PP population				
Protocol violation	4	1	1	6
Sponsor's and FDA's PP population	191	195	99	485

&: Patient(s) may have multiple reasons to be excluded from ITT, FITT, and PP populations.

*: Patient 407 in the reference treatment group was excluded from the sponsor's PP population due to protocol violation. This patient should be excluded from FITT due to not returning after visit 1.

Demographics and baseline

The mean age was 39.1 years and the age ranged from 18 to 80 years old in the FITT population. The table below shows the sex and race distribution for the FITT population. The age, gender, and race of patients were comparably distributed among the three treatment groups for the FITT and PP populations³.

	Terbinafine	Lamisil®	Placebo	Total
Gender				
Female	48	34	27	109
Male	147	162	73	382
Race				
White	142	133	71	346
Black	12	16	10	38
Hispanic	28	40	17	85
Others	13	7	2	22

An analysis of the frequencies and chi-square tests for homogeneity of signs/symptoms scores for the FITT and PP populations at the enrollment visit was performed. There were no significant differences between treatment arms for all the signs/symptoms scores for both populations at the enrollment visit.

Efficacy and equivalence Analyses

Primary endpoint: Therapeutic cure rate at visit 3/week 6.

³ Age was analyzed using a general linear model with treatment as a factor. Gender and race were analyzed using Chi-square tests.

Efficacy and equivalence analyses for primary endpoint – Therapeutic cure rate at visit 3

Population	Test* % successes (No. of successes /total)	Reference* % successes (No. of successes /total)	Placebo* % successes (No. of successes /total)	p-value# for Test vs. Placebo	p-value# for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
FITT	69.7 (136/195)	72.5 (142/196)	3.0 (3/100)	<0.001	<0.001		
PP	69.6 (133/191)	72.3 (141/195)	3.0 (3/99)			-10.8, 5.4	Yes

*: The rate of success equals the number of successes divided by the total number, then multiplied by 100.

#: The p-values were from Fisher's exact test (2-sided).

The two active treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the PP population for the therapeutic cure rate at visit 3.

Secondary endpoints: Mycological cure rate and clinical cure rate at visit 3/week 6.

Efficacy and equivalence analyses for secondary endpoints

Population /endpoint	Test % successes (No. of successes /total)	Reference % successes (No. of successes /total)	Placebo % successes (No. of successes /total)	p-value for Test vs. Placebo	p-value for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
FITT							
Mycological response	92.8 (181/195)	90.3 (177/196)	8.0 (8/100)	<0.001	<0.001		
Clinical response	74.4 (145/195)	79.6 (156/196)	41.0 (41/100)	<0.001	<0.001		
PP							
Mycological response	92.7 (177/191)	90.3 (176/195)	8.1 (8/99)	<0.001	<0.001	-2.8, 7.6	Yes
Clinical response	74.4 (142/191)	79.5 (155/195)	40.4 (40/99)	<0.001	<0.001	-12.7, 2.4	Yes

The two active treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the PP population for the mycological cure rate and clinical cure rate at visit 3.

Comments on the Sponsor's Analysis

The sponsor's analysis results using their ITT and PP populations for the therapeutic cure rate, mycological cure rate, and clinical cure rate were summarized in the FDA medical reviewer's report (page 18). The two active treatments were statistically significantly better than placebo for the ITT population and the equivalence test was passed for the PP population for the three cure rates at visit 3.

The differences between our results and the sponsor's were due to the adjustment of the ITT population to the FITT population in accordance with recommendations of the medical and statistical reviewers.

Safety

Please see the details in the OGD medical reviewer's report.

Conclusion

The two active treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the PP population for the **Therapeutic cure rate (both clinical cure and mycological cure)**, mycological cure rate, and clinical cure rate, at visit 3/week 6 (Follow-up visit).

Huaixiang Li 12/22/05
Huaixiang Li, Ph.D.
 Mathematical Statistician, QMR

Donald J. Schuirmann 12/21/05
Donald J. Schuirmann
 Expert Mathematical Statistician, QMR

Stella G. Machado 12/21/05
Stella G. Machado, Ph.D.
 Director, QMR

cc:

HFD-600 Dena R Hixon, Carol Y Kim, Debra M Catterson

HFD-705 Stella G. Machado, Donald J. Schuirmann, Huaixiang Li, QMR Chron

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-511

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

December 30, 2004

Office of Generic Drugs
Food and Drug Administration, CDER
Document Control Room
MPN II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Handwritten:
D. L. Baker
M. J. Baker
77-511
25 Feb 2005



Taro Pharmaceuticals U.S.A., Inc.

re: **Abbreviated New Drug Application**
Terbinafine Hydrochloride Cream, 1%

RECEIVED
JAN 03 2005
OGD / CDER

Dear Sir/Madam:

Taro Pharmaceuticals U.S.A., Inc. (Taro) submits today an original abbreviated new drug application (ANDA) seeking approval to market Terbinafine Hydrochloride Cream, 1% which is bioequivalent to the reference listed drug, Lamisil® (Terbinafine Hydrochloride) Cream, 1% manufactured by Novartis Consumer Health Inc. pursuant to NDA 20-980.

This ANDA is prepared in the ICH-CTD format, following the recommendations of the following guidance documents:

- Submitting Marketing Applications According to the ICH-CTD Format – General Considerations
- M4: Organization of the CTD
- M4E: The CTD – Efficacy
- M4Q: The CTD – Quality
- M4S: The CTD – Safety

This ANDA is comprised of 9 volumes. The volumes are distributed as follows:

Module 1: Administrative and Prescribing Information (1 volume)
Module 2: Common Technical Document Summaries (1 volume)
Module 3: Quality (3 volumes)
Module 4: Non-clinical study reports (not applicable)
Module 5: Clinical safety reports (4 volumes)

Taro Pharmaceuticals U.S.A., Inc., is filing archival, review and field copies as follows:

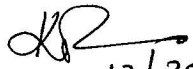
Archival Copy (9 copies)	Blue Jackets: Modules 1-5
Review Copy	
Quality (5 volumes)	Red Jackets: Modules 1, 2, and 3
Clinical – Bioequivalency (4 volumes)	Orange Jackets: Modules 1, 2, and 5
Clinical – Safety and Efficacy, Clinical	Not Applicable

Review	
Clinical – Safety and Efficacy, Statistical Review	Not Applicable
Field Copy (4 volumes)	Burgundy Jackets: Modules 1 and 3
Method Validation Package (1 volume, 3 copies)	Separately bound folders: Module 3.2.R.2

Taro hereby certifies that the 'field copy' is a true copy of the technical sections of the ANDA (copy: this letter, 356h form, 'true copy' certification). This 'field copy' is contained in burgundy folders. An additional three (3) copies of the method validation reports are included in a separate folder.

If you have any questions regarding this application, please contact the undersigned at 914-345-9001, ext 6298.

Sincerely,


12/30/04

Kalpana Rao
Vice President, Regulatory Affairs (Global)
Taro Pharmaceuticals U.S.A., Inc.

**BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS**

ANDA# 77-511 FIRM NAME Taro Pharmaceuticals USA, Inc.

DRUG NAME Terbinafine HCl Cream, 1%

DOSAGE FORM Cream

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	Study meets statutory requirements
☐	Study does NOT meet statutory requirements
	Reason:
☐	Waiver meets statutory requirements
☐	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: ☒ COMPLETE ☐ INCOMPLETE

Reviewed by:

Krista M. Sordani Date: 2/4/05
Reviewer

Dena R. Hixon MD Date: 2/4/05
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	X				
Summary of Study	X				
Clinical Site (s)	X				
Study Investigator (s)	X				
List of subjects included in PP/ (M)ITT populations per treatments	X				
List of subjects excluded/ from PP/ (M)ITT per treatments	X				
Reasons for discontinuation from the study if discontinued	X				
Adverse Events	X				
Concomitant Medications	X				
Individual subject's scores/data per visit	X				
Pre-screening of Patients	X				
IRB Approval	X				
Consent Forms	X				
Randomization Schedule	X				
Protocol Deviations	X				
Case Report Forms	X				
PD Data Disk (or Elec Subm)	X				EDR
Study Results	X				
Clinical Raw Data/ Medical Records	X				
Composition	NA				In Chemistry Section

BioStudy Lot Numbers	UA				} In Chemistry Section.
Date of Manufacture	UA				
Exp. Date of RLD	UA				
Statistical Reports	X				
Defined BE endpoints	X				
Summary results provided by the firm indicate studies pass BE criteria	X				Primary Endpoint is Therapeutic Cure at Week 6. CI: -10.8, 5.4
Summary results provided by the firm indicate superiority of the active treatments over the vehicle/placebo	X				$p < 0.001$ for both test and reference compared to placebo.
Waiver requests for other strengths / supporting data	N/A				

Additional Comments regarding the ANDA:

OGD provided protocol comments to Taro on August 18, 2004. The firm stated that after they received comments from OGD, they significantly changed their protocol. The first patient was not enrolled into the protocol was finalized.

This ANDA meets bioequivalence confidence intervals for the primary endpoint and is acceptable from a clinical standpoint.

ANDA 77-511

Taro Pharmaceuticals U.S.A. Inc.
Attention: Kalpana Rao
5 Skyline Drive
Hawthorne, NY 10532

FEB 25 2005

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Terbinafine Hydrochloride Cream, 1%

DATE OF APPLICATION: December 30, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 3, 2005

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Benjamin Danso
Project Manager
(301) 827-5848

Sincerely yours,



Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-511

cc: DUP/Jackets

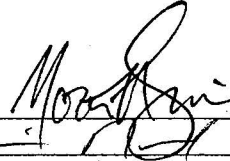
HFD-600/Division File

Field Copy

HFD-92

Endorsement:

HFD-615/MShimer, Chief, RSB



date 25 Feb 05

HFD-615/IMargand, CSO

date 2/25/05

Word File V:\Firmsnz\Taro\Ltrs&rev\7751.ack

F/T 2/24/05

ANDA Acknowledgment Letter!

ANDA 77-511 Final Check List for Branch Chief

- ☒ 1) Check letter date and stamp date of ANDA vs. drafted letter.
- ☒ 2) Check for any NC arriving post stamp date but prior to Reg. Review.
- ☒ 3) Check for gross errors in letter.
- ☒ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)
- ☒ 5) Check address and contact person on letter vs. 356h.
- ☒ 6) Check for any t-cons and verify date and correspondence date.
- ☒ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.
- ☒ 8) Check for any comments or problems raised by reviewer on Check List.
- ☒ 9) If first generic, copy BE review and file.
- ☒ 10) Sign Check List.
- ☒ 11) Check electronic Orange Book to verify current patent information and correct RLD. *Lamisil Cera*
- ☒ 12) Check for MOU patents
- ☒ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.
- ☒ 14) Review Basis for Submission. *Lamisil 20-980*
- ☒ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer. *PII → 534 app 12/30/06*)
- ☒ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.
- ☒ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature. _____
- ☒ 18) Pull USP information. (USP ☒ yes ☐ no)
- ☒ 19) Final Grammar review on letter.
- ☒ 20) Verify information in OGD Patent Tracking System.
- ☒ 21) EES slip.
- ☒ 22) Document in record book.

Signature

Martin H. Gunc

date

25 Feb 2005

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-511

FIRM NAME: TARO PHARMACEUTICALS U.S.A., INC.

RELATED APPLICATION(S): SEE 77-423 FOR
TERBINAFINE HYDROCHLORIDE TABLETS 250 MG FROM
TARO PHARMACEUTICALS (PN 12/6/04) RLD LAMISIL

First Generic Product Received? YES

Bio Assignments:

☒ BPH

☒ BCE

☒ BST

☐ BDI

☐ Micro Review

DRUG NAME: TERBINAFINE HYDROCHLORIDE

DOSAGE FORM: CREAM, 1 %

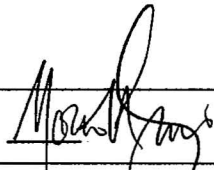
Random Queue: 5

Chem Team Leader: Liu, Shing

PM: Benjamin Danso

Labeling Reviewer: Ruby Wu

Letter Date: DECEMBER 30, 2004		Received Date: JANUARY 3, 2005	
Comments: EC – 1 YES		On Cards: YES	
Therapeutic Code:			
Archival Format: PAPER		Sections I (356H Sections per EDR Email)	
Review copy: YES		E-Media Disposition: YES SENT TO EDR	
Not applicable to electronic sections			
Field Copy Certification (Original Signature)			
Methods Validation Package (3 copies PAPER archive)		YES	
(Required for Non-USP drugs)			
Cover Letter YES		Table of Contents YES	
PART 3 Combination Product Category N Not a Part3 Combo Product			
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm			

Reviewing CSO/CST Iain Margand 		Recommendation:	
Date 2/24/05		☒ FILE ☐ REFUSE to RECEIVE	
Supervisory Concurrence/Date: 		Date: 25 Feb 2005	
ADDITIONAL COMMENTS REGARDING THE ANDA:			
Top 200 Drug Product:			

Sec. I	Signed and Completed Application Form (356h) (Statement regarding Rx/OTC Status)	☒
Sec. II	Basis for Submission NDA# : 20-980 Ref Listed Drug: LAMISIL Firm: NOVARTIS CONSUMER HEALTH INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☒
Sec. III	Patent Certification 1. Paragraph: III patent '534 2. Expiration of Patent: 12/30/2006 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? Exclusivity Statement: YES	☒
Sec. IV	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use OK 2. Active ingredients OK 3. Route of administration OK 4. Dosage Form OK 5. Strength OK	☒
Sec. V	Labeling (Mult Copies N/A for E-Submissions) 1. 4 copies of draft (each strength and container) or 12 copies of FPL Y 2. 1 RLD label and 1 RLD container label Y 3. 1 side by side labeling comparison with all differences annotated and explained Y 4. Was a proprietary name request submitted? NO (If yes, send email to Labeling Rvwr indicating such.)	☒
Sec. VI	Bioavailability/Bioequivalence 1. Financial Certification (Form FDA 3454) and Disclosure Statement (Form 3455) YES 2. Request for Waiver of In-Vivo Study(ies): NA 3. Formulation data same? (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) N/A 4. Lot Numbers of Products used in BE Study(ies): S182-54787 5. Study Type: IN-VIVO BE STUDY WITH C/EndPts (Continue with the appropriate study type box below)	☒
Study Type	IN-VIVO PK STUDY(IES) (i.e., fasting/fed/sprinkle) NA a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted: NA c. In-Vitro Dissolution: NA	☐

Study Type	IN-VIVO BE STUDY with CLINICAL ENDPOINTS YES/BIO STU (Bio performed first generic review) a. Properly defined BE endpoints (eval. by Clinical Team) Y b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) Y c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) Y d. EDR Email: Data Files Submitted YES SENT TO EDR	☒
Study Type	TRANSDERMAL DELIVERY SYSTEMS NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	NASALLY ADMINISTERED DRUG PRODUCTS NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES) NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	Components and Composition Statements 1. Unit composition and batch formulation batch – 3.2.P.3.2 unit – 2.3.P.1 2. Inactive ingredients as appropriate Excipients are acceptable per IIG	☒

Sec. VIII	Raw Materials Controls 1. Active Ingredients a. Addresses of bulk manufacturers Y b. Type II DMF authorization letters or synthesis DMF# (b) (4) c. COA(s) specifications and test results from drug substance mfg(s) Y d. Applicant certificate of analysis Y e. Testing specifications and data from drug product manufacturer(s) Y f. Spectra and chromatograms for reference standards and test samples Y g. CFN numbers 2. Inactive Ingredients a. Source of inactive ingredients identified 3.2.P.4.1 b. Testing specifications (including identification and characterization) Y c. Suppliers' COA (specifications and test results) Y d. Applicant certificate of analysis Y	☒
Sec. IX	Description of Manufacturing Facility 1. Full Address(es) of the Facility(ies) YES 2. CGMP Certification: YES 3. CFN numbers	☒
Sec. X	Outside Firms Including Contract Testing Laboratories 1. Full Address Y 2. Functions Y 3. CGMP Certification/GLP Y 4. CFN numbers	☒
Sec. XI	Manufacturing and Processing Instructions 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) 3.2.P.3.3 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) kg 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Filter validation (if aseptic fill) N/A 5. Reprocessing Statement Y	☒
Sec. XII	In-Process Controls 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation Ty: (b) (4) kg 2. In-process Controls - Specifications and data Y Ay: (b) (4) kg packaged: (b) (4)	☒
Sec. XIII	Container 1. Summary of Container/Closure System (if new resin, provide data) (b) (4) 2. Components Specification and Test Data (Type III DMF References) Y 3. Packaging Configuration and Sizes (b) (4) 12g, 15g, 24g and 30g tubes 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒

Sec. XIV	Controls for the Finished Dosage Form 1. Testing Specifications and Data Y 2. Certificate of Analysis for Finished Dosage Form Y	☒
Sec. XV	Stability of Finished Dosage Form 1. Protocol submitted Y 2. Post Approval Commitments Y 3. Expiration Dating Period 24 months 4. Stability Data Submitted a. 3 month accelerated stability data Y b. Batch numbers on stability records the same as the test batch S182-54787	☒
Sec. XVI	Samples - Statement of Availability and Identification of: 1. Drug Substance 2. Finished Dosage Form 3. Same lot numbers	☒
Sec. XVII	Environmental Impact Analysis Statement	☒
Sec. XVIII	GDEA (Generic Drug Enforcement Act)/Other: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) N/A 4. Field Copy Certification (original signature) YES	☒



Taro Pharmaceuticals U.S.A., Inc.

March 9, 2005

Office of Generic Drugs
Food and Drug Administration, CDER
Document Control Room
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/AC

RE: Terbinafine Hydrochloride Cream, 1%
Amendment to Abbreviated New Drug Application
ANDA 77-511

Dear Sir/Madam:

Taro Pharmaceuticals U.S.A., Inc. (Taro) submits today an amendment to our original abbreviated new drug application (ANDA) seeking approval to market Terbinafine Hydrochloride Cream, 1% using the active drug substance, Terbinafine Hydrochloride from the alternate manufacturer, (b) (4)

(b) (4)

This amendment is prepared in the ICH-CTD format, following the recommendations of the following guidance documents:

- Submitting Marketing Applications According to the ICH-CTD Format – General Considerations
- M4: Organization of the CTD
- M4Q: The CTD – Quality

RECEIVED

MAR 10 2005

OGD / CDER

This amendment is comprised of 1 volume. The volume consists of the following modules:

Module 1: Administrative and Prescribing Information
Module 2: Common Technical Document Summaries
Module 3: Quality

Taro Pharmaceuticals U.S.A., Inc., is filing archival, review and field copies as follows:

Archival Copy (1 volume)	Blue Jackets: Modules 1-3
Review Copy	
Quality (1 volume)	Red Jackets: Modules 1- 3
Field Copy (1 volume)	Burgundy Jackets: Module 3

Taro hereby certifies that the 'field copy' is a true copy of the technical sections of the amendment to the ANDA. This 'field copy' is contained in burgundy folders.

If you have any questions regarding this application, please contact the undersigned at 914-345-9001, ext 6298.

Sincerely,



 Kalpana Rao
Vice President, Regulatory Affairs (Global)
Taro Pharmaceuticals U.S.A., Inc.

May 25, 2005

ORIG AMENDMENT

N/A



Taro Pharmaceuticals U.S.A., Inc.

Ruby Wu
Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA #77-511**
Terbinafine Hydrochloride Cream, 1% (OTC)
Labeling Amendment

Dear Ms. Dillahunt:

Reference is made to Taro Pharmaceuticals U.S.A., Inc.'s Abbreviated New Drug Application (ANDA), submitted on December 30, 2004, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Terbinafine Hydrochloride Cream, 1% (OTC). Reference is also made to the labeling deficiency letter dated May 11, 2005, in which the following was noted:

1. GENERAL COMMENTS

- a. Revise "Terbinafine Hydrochloride 1% Cream" to read "Terbinafine Hydrochloride Cream 1%".
- b. In order for us to verify your compliance with the labeling format requirements of 21CFR 201.66, please submit a format legend for each size of your container and carton labels.

2. CONTAINER ^(b)₍₄₎ 12 g, 15 g, 24 g, and 30 g tubes)

Refer to GENERAL COMMENTS

3. CARTON (one tube)

- a. Refer to GENERAL COMMENTS
- b. 12 g and 15 g Cartons: In the electronic submission, text is cut-off. Please realign the horizontal barlines (refer to attachment).

4. CONSUMER EDUCATIONAL BROCHURE:

- a. Refer to GENERAL COMMENT 1.a
- b. Picture #1: add the caption "1 week between the toes"

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

RECEIVED

MAY 26 2005

OGD / CDER

Response

We have made the requested changes and enclosed please find:

- **12 Final Printed tube and carton labels (b) (4) 12 g, 15 g, 24 g, and 30 g)**
- **12 Final Printed Consumer Educational Brochures**

In addition, and in accordance with 21CFR 314.94(a)(8)(iv), we are providing a side-by-side comparison of one size of our previously submitted tube and carton with our current tube and carton and of our previously submitted Consumer Educational Brochures with our current Consumer Educational Brochure. We are also submitting electronically a Word document containing the text of the Consumer Educational Brochure and a CD with PDF files of each of the labels and labeling.

This concludes our response to the Agency's labeling deficiency letter of May 11, 2005. If you should have any questions regarding this submission, please do not hesitate to contact the undersigned at (914) 345-9001 x6298.

Sincerely,



For Kalpana Rao
Vice President, Regulatory Affairs (Global)

MINOR AMENDMENT

ANDA 77-511

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUN 30 2005



APPLICANT: Taro Pharmaceuticals U.S.A, Inc.

TEL: 914-345-9001

ATTN: Kalpana Rao

FAX: 914-593-0078

FROM: Benjamin Danso

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 30, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Terbinafine Hydrochloride Cream, 1%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Please include in response.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

9/30/05
[Signature]



Taro Pharmaceuticals U.S.A., Inc.

August 23, 2005

ORIG AMENDMENT

NIAM

Office of Generic Drugs
Food and Drug Administration, CDER
Document Control Room
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855-2773

RE: Terbinafine Hydrochloride Cream, 1%
ANDA 77-511
Response to **Minor Amendment** dated June 30, 2005

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product submitted on December 30, 2004 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

Reference is also made to the Minor Amendment letter dated June 30, 2005, stating that the application was deficient and, therefore not approvable under Section 505 of the Food, Drug and Cosmetic Act. Listed below are the comments raised in the Minor Amendment letter followed by our responses.

Comment 1.

The DMF [REDACTED] (b) (4), is currently inadequate. The DMF holder has been notified. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiencies has been submitted to the agency.

Response

[REDACTED] (b) (4). A copy of the cover letter is provided.

RECEIVED

AUG 24 2005

OGD/CDER

Comment 2.

Regarding the drug substance specifications, we have the following comments:

- a) Please revise the specification to include (b) (4) content and submit the method.**
- b) Please revise the specification to include Clarity of Solution.**
- c) Please revise the specification for 'any individual unknown impurities' from NMT (b) (4)% to NMT (b) (4)%.**
- d) Please revise the specification to include particle size.**
- e) Please submit a revised drug substance certificate of analysis with aforementioned revisions.**

Response

- a) The specification has been revised to include a (b) (4) Content' test.*

With the addition of the (b) (4) Content test, the (b) (4) Identification test has been replaced with an HPLC Identification test. A copy of the revised specification is provided in Appendix 1. The (b) (4) content method used was adapted from Taro Pharmaceutical Laboratories Inc. A copy of the method is provided in Appendix 2.

- b) The specification has been revised to include 'Clarity of Solution'. A copy of the revised specification is provided in Appendix 1. A copy of the Clarity of Solution test method is provided in Appendix 2.*
- c) The specification for 'any individual unknown impurities' has been revised from 'NMT (b) (4)% to NMT (b) (4)%. A copy of the revised specification is provided in Appendix 1.*
- d) A specification for particle size will not be proposed. The particle size does not impact the manufacture of the Terbinafine HCl Cream, 1% as the terbinafine HCl drug substance is (b) (4)*
- e) A revised drug substance certificate of analysis with the aforementioned revisions is provided in Appendix 3.*

Please note that the Assay specification was tightened from (b) (4)% to (b) (4)% to be consistent with the revised Taro Pharmaceutical Laboratories Inc.'s specification for the Assay of Terbinafine HCl.

Comment 3.

(b) (4) is listed as a residual solvent in your drug substance specifications. In Section 3.2.S.4.1 the results were not reported on the CoA for drug substance manufactured by Taro. Please explain.

Response

(b) (4) is not present in Terbinafine HCl manufactured by Taro Pharmaceutical Laboratories Inc., but is present in the (b) (4). The specification provided in Appendix 1 was revised to identify the applicable drug substance manufacturer for each solvent listed.

Comment 4.

Regarding your drug product release and stability, please set the impurity specifications based on ICH Q3(B). Please set the individual unidentified degradation products as NMT the identification threshold ((b) (4) %).

Response

The following proposed impurity specification for the release and stability of the drug product has been revised based on the ICH Q3(B).

Using a Total Daily Intake (TDI) of 34 mg/day of terbinafine HCl, the ICH Q3(B) presents the following thresholds:

	Maximum daily dose	ICH Q3(B) recommended limits	Proposed limit		
			Degradation products	For Release	For Stability
<u>Reporting Thresholds:</u>	≤ 1 g	0.1%			
<u>Identification Thresholds:</u>	> 10 mg – 2 g	0.2% or 2 mg TDI (equivalent to 5.9%)	Individual unknown	NMT (b) (4)	NMT %
<u>Qualification Thresholds:</u>	10 mg – 100 mg	0.5% or 200 µg TDI (equivalent to 0.59%)	Known degradants	NMT (b) (4) %	NMT (b) (4) %

The proposed limit for release of the finished product is tighter than that recommended by the ICH Q3(B), the proposed limit for stability of the finished product is as per the ICH Q3(B).

The original specifications provided in the ANDA were as follows:

Degradation products	For Release	For Stability
Individual unknown	NMT (b) (4) %	NMT (b) (4) %
Known degradants	NMT (b) (4) %	NMT (b) (4) %

The TDI was calculated as follows:

The recommended treatment period for Lamisil AT is 7 days.

If a patient used the entire tube of the largest size (24 g tube) for a 7 day treatment, TDI of cream = 24g/7days = 3.4g/day of the cream. Since the concentration of active in the cream is 1%, each 1g of cream has 10 mg of API. Hence, TDI of API = 3.4g/day of cream x 10 mg API/ g of cream = 34 mg/day of terbinafine API.

In addition to the revision of the impurity specification, the in-process, release, and stability specifications were revised to finalize the limit for viscosity. The tentative limit (b) (4) cps is now the established limit.

Provided in Appendix 4 are the revised in-process, finished product release and stability specifications.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response.

1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
2. Please provide all available long-term stability data to update your studies.
3. Your labeling responses, dated May 26, 2005, are under review and any deficiencies will be communicated to you.
4. All facilities referenced in your application should have a satisfactory compliance evaluation by our Division of Compliance at the time of approval.

Response to B. above

1. *We acknowledge that the bioequivalence information is pending review and be there any deficiencies, it will be communicated separately.*
2. *All available long-term stability data has been provided in Appendix 5. The following data is available:*
 - *9 month RT data for Lot S182-55236 (manufactured with Taro Israel API)*
 - *12 month RT data for Lot S182-54787 (manufactured with (b) (4))*
3. *We acknowledge that our labeling responses, dated May 26, 2005 is under review.*
4. *We acknowledge that all facilities referenced in our application need to have a satisfactory compliance evaluation by the Division of Compliance at the time of approval.*

This Minor Amendment is being submitted in two copies. A third (Field copy) is also enclosed. Taro hereby certifies that the 'field copy' is a true copy of the technical sections of the amendment to the ANDA.

We trust that the deficiencies raised have been addressed in a complete and satisfactory manner. If you have any questions regarding this application, please contact us at:

Taro Pharmaceuticals U.S.A., Inc.
Attn: Kalpana Rao, VP, Regulatory Affairs (Global)
3 Skyline Drive
Hawthorne, New York 10532
Tel: 914-345-9001, ext 6298
Fax: 914-593-0078

Sincerely,



for Kalpana Rao
Vice President, Regulatory Affairs (Global)

ANDA APPROVAL SUMMARY

ANDA: 77-511	CHEMIST: Kathy P. Woodland	DATE: September 23, 2005
DRUG PRODUCT: Terbinafine Hydrochloride Cream, 1%		
FIRM: Taro Pharmaceuticals U.S.A., Inc.		
DOSAGE FORM: Cream	STRENGTH: 1%	
cGMP: Satisfactory, February 28, 2005, S. Adams		
BIO: PENDING		
VALIDATION - (Description of dosage form same as firm's): Not required		
STABILITY: The containers in the stability studies are identical to those in the container section.		
LABELING: Acceptable, Ruby Wu, July 13, 2005		
STERILIZATION VALIDATION (If applicable): N/A		
SIZE OF BIO BATCH (Firm's source of NDS ok?): (b) (4) is the source of drug substance		
SIZE OF STABILITY BATCHES (If different from bio batch, were they Manufactured via the same process?): The exhibit batches were (b) (4) kg each, made from Taro (b) (4) drug substance.		
PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?: The proposed production batch is (b) (4) kg		
Signature of chemist: Kathy P. Woodland		Signature of supervisor: J. B. B. 10-26-05

V:\FIRMSNZ\TARO\LTRS&REV\77511.APSUM.DOC

Danso, Benjamin

From: Grace, John F
Sent: Tuesday, January 24, 2006 9:19 AM
To: Wu, Ruby (Chi-Ann); Danso, Benjamin
Subject: RE: ANDA 77-511 FPL sign off

I concur.

-----Original Message-----

From: Wu, Ruby (Chi-Ann)
Sent: Monday, January 23, 2006 1:35 PM
To: Danso, Benjamin; Grace, John F
Subject: ANDA 77-511 FPL sign off

John,

Sorry! I was in a hurry to go to a meeting and didn't check my facts. The product is OTC and I forgot to click the OTC box when I checked the orange book.

I checked the OB (OTC section), USP, and DSS. The labeling approval summary signed off 7/15/2005 remains acceptable.

Ruby

-----Original Message-----

From: Wu, Ruby (Chi-Ann)
Sent: Monday, January 23, 2006 11:03 AM
To: Danso, Benjamin; Grace, John F
Subject: FW: ANDA 77-511 FPL sign off

John,

The RLD is now in the DISCONTINUED section of the orange book. Do we need to know if it was discontinued for safety/efficacy reasons?

There is no other terbinafine hcl cream applications approved.

Drug product not subject to USP monograph.

Ruby

-----Original Message-----

From: Danso, Benjamin
Sent: Friday, January 20, 2006 3:26 PM
To: Wu, Ruby (Chi-Ann); Grace, John F
Subject: ANDA 77-511 FPL sign off

Ruby/ John,

Is the attached fpl sign off doc still in good standing for TA to move fwd? Your response to this e-mail will represent your final signatures on the TA letter.

Thanks

<< File: 77511.fpl.pdf >>

LT Benjamin Danso, Pharm.D.
7500 Standish Pl
OGD/HFD-617/MPN2
Rockville, MD 20855
DansoB@CDER.FDA.GOV

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-511 Applicant Taro Pharmaceuticals U.S.A. Inc.
Drug Terbinafine Hydrochloride Cream Strength(s) 1%

APPROVAL ☐ TENTATIVE APPROVAL ☒ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer
 Chief, Reg. Support Branch

Date 20 Jan 2006
 Initials MS

Date _____
 Initials _____

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☐
 (required if sub after 6/1/92) Pediatric Exclusivity System

RLD = _____ NDA# _____

Patent/Exclusivity Certification: Yes ☒ No ☐

Date Checked _____

If Para. IV Certification- did applicant

Nothing Submitted ☐

Notify patent holder/NDA holder Yes ☐ No ☐

Written request issued ☐

Was applicant sued w/in 45 days: Yes ☐ No ☐

Study Submitted ☐

Has case been settled: Yes ☐ No ☐

Date settled: _____

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes ☐ No ☐

Date of latest Labeling Review/Approval Summary 7/15/05

Any filing status changes requiring addition Labeling Review Yes ☐ No ☒

Type of Letter: _____

Comments:

PIII to 1534 app 12/30/06 : eligible for TAC only

2. Project Manager, Ben Danso Team 5
 Review Support Branch

Date 1-19-06
 Initials BD

Date _____
 Initials _____

Original Rec'd date 12-30-04

EER Status Pending ☒ Acceptable ☐ OAI ☐

Date Acceptable for Filing 1-03-05

Date of EER Status _____

Patent Certification (type) P III

Date of Office Bio Review 1-06-06

Date Patent/Exclus. expires 12-30-06

Date of Labeling Approv. Sum 7-15-05

Citizens' Petition/Legal Case Yes ☐ No ☒

Labeling Acceptable Email Rec'd Yes ☒ No ☐

(If YES, attach email from PM to CP coord)

Labeling Acceptable Email filed Yes ☒ No ☐

First Generic Yes ☒ No ☐ Date of Sterility Assur. App. _____

Methods Val. Samples Pending Yes ☐ No ☐

MV Commitment Rcd. from Firm Yes ☐ No ☐

Acceptable Bio reviews tabbed Yes ☒ No ☐ Modified-release dosage form: Yes ☐ No ☒

Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes ☐

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

Previously reviewed and tentatively approved ☐ Date _____

Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____

Comments:

3. David Read (PP IVs Only) Pre-MMA Language included ☐
 OGD Regulatory Counsel, Post-MMA Language Included ☐
 Comments:

Date _____
 Initials _____

4. Div. Dir./Deputy Dir.
 Chemistry Div. I II OR III
 Comments:

Date 1/31/05
 Initials PS

CAC is OK

REVIEWER:FINAL ACTION

5. Frank Holcombe First Generics Only
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

Date 2-14-06
Initials lh

For Frank

CME ok - Radhika Rajagopalan

6. Vacant
Deputy Dir., DLPS

Date _____
Initials _____

7. Peter Rickman
Director, DLPS

Date 2/14/06
Initials WR

Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒

Comments:

*IP III to the '534 patent TA only expires 12/30/2006
No exclusivity issues*

OR

Labeling acceptable per TA summary 7/15/2005

*Bio acceptable per office stud sign off 1/6/2006 (clinical endpoint study)
Applicant w/D alternate API manufacturer on 3/21/2006
No DSI needed*

EE R now acceptable 2/28/2005

TA only

8. Robert L. West
Deputy Director, OGD

Date _____
Initials _____

Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐

Comments:

9. Gary Buehler
Director, OGD
Comments:

Date 3/22/06
Initials GB

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐

10. Project Manager, Team Ben Danso
Review Support Branch

Date 3/22/06
Initials BD

Date PETS checked for first generic drug (just prior to notification to CDM)

Applicant notification:

140 Time notified of approval by phone 1:50 PM Time approval letter faxed

FDA Notification:

3/22/06 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Search results from the "OB_OTC" table for query on "020980."

Active Ingredient:	TERBINAFINE HYDROCHLORIDE
Dosage Form;Route:	CREAM; TOPICAL
Proprietary Name:	LAMISIL
Applicant:	NOVARTIS
Strength:	1%
Application Number:	020980
Product Number:	001
Approval Date:	Mar 9, 1999
Reference Listed Drug	Yes
RX/OTC/DISCN:	OTC
Patent and Exclusivity Info for this product:	View

[Return to Electronic Orange Book Home Page](#)

FDA/Center for Drug Evaluation and Research

Office of Generic Drugs

Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through December, 2005

Patent and Generic Drug Product Data Last Updated: January 18, 2006

Patent and Exclusivity Search Results from query on Appl No 020980 Product 001 in the OB_OTC list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020980	001	4755534	DEC 30,2006			<u>U-73</u>

Exclusivity Data**There is no unexpired exclusivity for this product.**

Additional information:

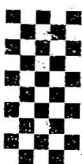
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
 2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
 3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
 4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.
-

[View a list of all patent use codes](#)[View a list of all exclusivity codes](#)[Return to Electronic Orange Book Home Page](#)

FDA/Center for Drug Evaluation and Research**Office of Generic Drugs****Division of Labeling and Program Support****Update Frequency:**Orange Book Data - **Monthly**Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through December, 2005

Patent and Generic Drug Product Data Last Updated: January 18, 2006



MAR. 21. 2006 3:49PM

TARO PHARMACEUTICAL

NO. 390
Taro Pharmaceuticals U.S.A., Inc.
3 Skyline Drive
Hawthorne, NY 10532

Tel (914)345-9001
Fax (914)593-0078

.....
facsimile transmittal

To: Benjamin Danso, Project Manager, OGD, CDER, FDA Fax: 301-594-0180

From: Kalpana Rao Date: 03/21/06
GVP, Regulatory Affairs (Global)
Taro Pharmaceuticals USA, Inc.

Re: **Gratuitous Amendment** Pages: 6 (including cover page)
ANDA 77-511
Terbinafine Hydrochloride Cream, 1%
Request for (b) (4)

CC:

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Taro Pharmaceuticals USA Inc. has submitted a Gratuitous amendment for the Abbreviated New Drug Application (ANDA 78-511) for Terbinafine Hydrochloride Cream, 1% requesting (b) (4)

Copy of the amendment is enclosed. The Gratuitous amendment has been mailed to the Agency via courier.

Should there be any questions or need for additional documents, please do not hesitate to contact the undersigned (914)345-9001x6298.

Sincerely,

Kavita Srivastava
for Kalpana Rao
GVP, Regulatory Affairs (Global)
Taro Pharmaceuticals U.S.A., Inc.

Enclosures

.....



Taro Pharmaceuticals U.S.A., Inc.

March 21, 2006

Attn: Benjamin Danso,
Project Manager
Office of Generic Drugs
Food and Drug Administration, CDER
Document Control Room
MPN II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA # 77-511, Terbinafine Hydrochloride Cream, 1%**
Gratuitous Amendment
Request for [REDACTED] (b) (4)

Dear Sir,

This is in reference to our Abbreviated New Drug Application for the above mentioned product submitted to the Agency on December 30, 2004. Reference is also made to the amendment dated March 9, 2005 and subsequent correspondence from the FDA dated June 30, 2005 followed by amendment dated August 12, 2005.

At this time, Taro Pharmaceuticals U.S.A., Inc. hereby submits a gratuitous amendment requesting [REDACTED] (b) (4)

[REDACTED] for this product without prejudice for further filing.

If there are any questions with regards to this amendment, please do not hesitate to contact us at:

Taro Pharmaceuticals U.S.A., Inc.
Attn: Kalpana Rao
Group Vice President, Regulatory Affairs (Global)
3 Skyline Drive
Hawthorne, NY 10532
Tel.: (914) 345-9001X6298
Fax: (914) 593-0078

Sincerely,

Kavita Srivastava

for

Kalpana Rao
Group Vice President, Regulatory Affairs (Global)

cc: FDA, Office of International Programs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Taro Pharmaceuticals USA, Inc.

DATE OF SUBMISSION

3/21/06

TELEPHONE NO. (Include Area Code)

914-345-9001

FACSIMILE (FAX) Number (Include Area Code)

914-593-0078

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

3 Skyline Drive
Hawthorne, NY 10532

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 77-511

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Terbinafine Hydrochloride Cream, 1%

PROPRIETARY NAME (trade name) IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

(E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride

CODE NAME (If any)

DOSAGE FORM:

Cream

STRENGTHS:

10 mg/g (1%)

ROUTE OF ADMINISTRATION:

Topical

(PROPOSED) INDICATION(S) FOR USE:

Treatment of athlete's foot.

APPLICATION DESCRIPTION

APPLICATION TYPE

(check one)

☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50)

☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

☐ 505 (b)(1)

☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Lamisil

Holder of Approved Application

Novartis consumer Health Inc.

TYPE OF SUBMISSION (check one)

☐ ORIGINAL APPLICATION

☒ AMENDMENT TO PENDING APPLICATION

☐ RESUBMISSION

☐ PRESUBMISSION

☐ ANNUAL REPORT

☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT

☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT

☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

☐ CBE

☐ CBE-30

☐ Prior Approval (PA)

REASON FOR SUBMISSION

Gratuitous Amendment-Request for

(b) (4)

PROPOSED MARKETING STATUS (check one)

☒ PRESCRIPTION PRODUCT (Rx)

☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS

☒ PAPER

☐ PAPER AND ELECTRONIC

☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Man/Pack/Controls: Taro Pharmaceuticals Inc., 130 East Dr., Brampton, ON, Canada (Establishment no. FCCA133); Controls:

(b) (4)

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See Attachment

This application contains the following items: (Check all that apply)

☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense. U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Kavita Srivastava for Kalpana Rao</i>	TYPED NAME AND TITLE Kalpana Rao, GVP Regulatory Affairs (Global)	DATE: 3/21/06
ADDRESS (Street, City, State, and ZIP Code) 3 Skyline Drive, Hawthorne, NY 10532		Telephone Number (914) 345-9001

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Attachment to Form FDA 356h**Cross References****DMF List**

Name	DMF No.	Function
		

(b) (4)



Taro Pharmaceuticals U.S.A., Inc.

March 21, 2006

N/AA

Attn: Benjamin Danso,
Project Manager
Office of Generic Drugs
Food and Drug Administration, CDER
Document Control Room
MPN II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA # 77-511, Terbinafine Hydrochloride Cream, 1%**
Gratuitous Amendment
Request for [REDACTED] (b) (4)

Dear Sir,

This is in reference to our Abbreviated New Drug Application for the above mentioned product submitted to the Agency on December 30, 2004. Reference is also made to the amendment dated March 9, 2005 and subsequent correspondence from the FDA dated June 30, 2005 followed by amendment dated August 12, 2005.

At this time, Taro Pharmaceuticals U.S.A., Inc. hereby submits a gratuitous amendment requesting [REDACTED] (b) (4)

[REDACTED] for this product without prejudice for further filing.

RECEIVED

MAR 22 2006

OGD / CDER

If there are any questions with regards to this amendment, please do not hesitate to contact us at:

Taro Pharmaceuticals U.S.A., Inc.
Attn: Kalpana Rao
Group Vice President, Regulatory Affairs (Global)
3 Skyline Drive
Hawthorne, NY 10532
Tel.: (914) 345-9001X6298
Fax: (914) 593-0078

Sincerely,

Kavita Srivastava

for

Kalpana Rao
Group Vice President, Regulatory Affairs (Global)

cc: FDA, Office of International Programs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Taro Pharmaceuticals USA, Inc.	DATE OF SUBMISSION 3/21/06
TELEPHONE NO. (Include Area Code) 914-345-9001	FACSIMILE (FAX) Number (Include Area Code) 914-593-0078
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 3 Skyline Drive Hawthorne, NY 10532	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 77-511		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Terbinafine Hydrochloride Cream, 1%		PROPRIETARY NAME (trade name) IF ANY
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride		CODE NAME (If any)
DOSAGE FORM: Cream	STRENGTHS: 10 mg/g (1%)	ROUTE OF ADMINISTRATION: Topical
(PROPOSED) INDICATION(S) FOR USE: Treatment of athlete's foot.		

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)		
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION		
Name of Drug	Holder of Approved Application	
Lamisil	Novartis consumer Health Inc.	
TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER		
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: N/A		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)		
REASON FOR SUBMISSION Gratuitous Amendment-Request for (b) (4)		
PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED	THIS APPLICATION IS	
1	☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC	
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
Man/Pack/Controls: Taro Pharmaceuticals Inc., 130 East Dr., Brampton, ON, Canada (Establishment no. FCCA133); Controls: (b) (4)		

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See Attachment

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This application contains the following items: (Check all that apply)

☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Kavita Divastava for Kalpana Rao</i>	TYPED NAME AND TITLE Kalpana Rao, GVP Regulatory Affairs (Global)	DATE: 3/21/06
ADDRESS (Street, City, State, and ZIP Code) 3 Skyline Drive, Hawthorne, NY 10532		Telephone Number (914) 345-9001

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Attachment to Form FDA 356h

Cross References

DMF List

<u>Name</u>	DMF No.	Function
(b) (4)		

A4.1



Taro Pharmaceuticals U.S.A., Inc.

October 4, 2006

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773
USA

ORIG AMENDMENT
N/AM

RE: **ANDA 77-511**
Terbinafine Hydrochloride Cream, 1%
Minor Amendment – Final Approval Requested

Dear Sir or Madam,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, submitted on December 30, 2004 and tentatively approved on March 22, 2006.

At this time Taro would like to request that a final approval be granted for the above mentioned ANDA. Taro submitted the above-referenced ANDA containing a paragraph III certification to the Patent No. 4755534 which will expire on December 30, 2006. The Certification stated that Taro Pharmaceuticals USA Inc. will not market its Terbinafine HCl Cream, 1% prior to the expiration of the patent.

As recommended in the Tentative Approval Letter, in order to reactivate our application prior to the final approval, we are hereby submitting a "Minor Amendment – Final Approval Requested" 90 days prior to the date that our application will be approved, i.e., December 30, 2006.

In addition to requesting final approval of this ANDA, we would also like to inform the Agency of the following minor changes made to the analytical method SOP A-1164-2 "HPLC Assay Method for the Quantitation of Terbinafine HCl and Its Related Impurities in Terbinafine HCl Drug Substance and Terbinafine HCl Cream, 1%" (copy attached):

a.

(b) (4)

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b.

(b) (4)



With the exception of the above mentioned changes, there are no other revisions to the labeling or Chemistry, Manufacturing and Controls information approved in the ANDA.

This concludes our request for final approval. If there are any questions, with regards to this amendment, please contact the undersigned at 914-345-9001, Ext. 6298.

Sincerely,



for Kalpana Rao
GVP, Regulatory Affairs (Global)
Taro Pharmaceuticals U.S.A., Inc.

cc. FDA, Office of International Programs



Taro Pharmaceuticals U.S.A., Inc.

October 4, 2006

Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, Maryland
U.S.A. 20852

Attention: FDA, Office of International Programs

Ref: **ANDA 77-511**
Terbinafine Hydrochloride Cream, 1%
Minor Amendment – Final Approval Requested

Dear Sir/Madam:

Taro Pharmaceuticals U.S.A., Inc. hereby submits and certifies that the enclosed field copy is a true copy of the technical information provided in the above referenced Minor Amendment – Final Approval Requested.

If there are any questions in regards to this documentation, please do not hesitate to contact the undersigned at 914-345-9001, Ext. 6298.

Sincerely,

for A handwritten signature in cursive script, appearing to read "Kalpana Rao".

Kalpana Rao
GVP, Regulatory Affairs (Global)
Taro Pharmaceuticals U.S.A., Inc.

RECEIVED
OCT 05 2006
OGD / CDER

March 30, 2007

Food and Drug Administration
Office of Generic Drugs,
Metro Park North II,
Room # 150,
7500 Standish Place,
Rockville, MD 20855



Taro Pharmaceuticals U.S.A., Inc.

RE: **ANDA 77-511**
Terbinafine Hydrochloride Cream, 1%
Minor Amendment – Final Approval Requested

ORIG AMENDMENT

N-AM

Dear Sir or Madam,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, submitted on December 30, 2004 and tentatively approved on March 22, 2006. Reference is also made to the Minor Amendment – Final Approval Requested dated October 4, 2006.

At this time Taro Pharmaceuticals U.S.A., Inc., (Taro) would like to request that a final approval be granted for the above mentioned ANDA. Taro submitted the above-referenced ANDA containing a paragraph III certification to the Patent No. 4755534 which expired on December 30, 2006. Pediatric exclusivity was granted to patent No. 4755534*PED which will expire June 30, 2007.

As recommended in the Tentative Approval Letter, in order to reactivate our application prior to the final approval, we are hereby submitting a "Minor Amendment – Final Approval Requested" 90 days prior to the date that our application will be approved, i.e., June 30, 2007.

Please note that there are no revisions to the labeling or Chemistry, Manufacturing and Controls information approved in the ANDA and subsequent amendments.

This concludes our request for final approval. If there are any questions, with regard to this amendment, please contact the undersigned at 914-345-9001, Ext. 6298.

Sincerely,

Kalpana Rao
for Kalpana Rao
GVP, Regulatory Affairs (Global)
Taro Pharmaceuticals U.S.A., Inc.

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cc. FDA, Office of International Programs



Taro Pharmaceuticals U.S.A., Inc.

March 30, 2007

Food and Drug Administration
Office of Generic Drugs,
Metro Park North II,
Room # 150,
7500 Standish Place,
Rockville, MD 20855

Attention: FDA, Office of International Programs

RE: **ANDA 77-511**
Terbinafine Hydrochloride Cream, 1%
Minor Amendment – Final Approval Requested

Dear Sir/Madam:

Taro Pharmaceuticals U.S.A., Inc. hereby submits and certifies that the enclosed field copy is a true copy of the technical information provided in the above referenced Minor Amendment – Final Approval Requested.

If there are any questions in regards to this documentation, please do not hesitate to contact the undersigned at 914-345-9001, Ext. 6298.

Sincerely,

A handwritten signature in cursive script, appearing to read "Kalpana Rao".

for Kalpana Rao
GVP, Regulatory Affairs (Global)
Taro Pharmaceuticals U.S.A., Inc.

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : ANDA 77511/000 Sponsor: TARO PHARMS (US)
Org Code : 600 5 SKYLINE DR
Priority : HAWTHORNE, NY 10532

Stamp Date : 03-JAN-2005 Brand Name :
PDUFA Date : Estab. Name: TERBINAFINE HYDROCHLORI
Action Goal : Generic Name:
District Goal: 03-DEC-2005 Dosage Form: (CREAM)
Strength : 10 MG/G (1%)

FDA Contacts: B. DANSO Project Manager (HFD-617) 301-8
27-5763
A. MUELLER Team Leader (HFD-623) 301-8
27-5848

Overall Recommendation: ACCEPTABLE on 28-FEB-2005 by S. ADAMS (HFD-322) 3
01-827-9051

Establishment : CFN : FEI :

(b) (4)

DMF No: (b) (4)

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-FEB-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-FEB-05
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9614240 FEI : 3002808384
TARO PHARMACEUTICALS INC
130 EAST DRIVE
BRAMPTON, ONTARIO, CA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : OIN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-FEB-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment :

CFN : (b) (4)

FEI : (b) (4)

(b) (4)

DMF No:

AADA:

Responsibilities:

FINISHED DOSAGE OTHER TESTER

Profile : CTL

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-FEB-05

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment :

CFN : (b) (4)

FEI : (b) (4)

(b) (4)

DMF No:

AADA:

Responsibilities:

FINISHED DOSAGE OTHER TESTER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : ANDA 77511/000

Sponsor: TARO PHARMS (US)

Org Code : 600

5 SKYLINE DR

Priority :

HAWTHORNE, NY 10532

Stamp Date : 03-JAN-2005

Brand Name :

PDUFA Date :

Estab. Name: TERBINAFINE HYDROCHLO

IDE

Action Goal :

Generic Name:

District Goal: 03-DEC-2005

Dosage Form: (CREAM)

Strength : 10 MG/G (1%)

FDA Contacts: B. DANSO
-827-5763

Project Manager (HFD-617) 301

A. MUELLER
-827-5848

Team Leader (HFD-623) 301

Overall Recommendation:
301-827-9051

ACCEPTABLE on 28-FEB-2005 by S. ADAMS (HFD-322)

*One site .55% PENDING**2/16/06
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Establishment : CFN :

FEI :

(b) (4)

DMF No:

(b) (4)

AADA:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE
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Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO (b) (4)
Milestone Date: 28-JUN-05
:
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Establishment : CFN : 9614240 FEI : 3002808384
TARO PHARMACEUTICALS INC
130 EAST DRIVE
BRAMPTON, ONTARIO, CA

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-FEB-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-FEB-05
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

DMF No:

AADA:

DMF No:

AADA:

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Last Milestone: OC RECOMMENDATION

Milestone Date: 25-FEB-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

20-SEP-2005

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : ANDA 77511/000 Sponsor: TARO PHARMS (US)
Org Code : 600 5 SKYLINE DR
Priority : HAWTHORNE, NY 10532

Stamp Date : 03-JAN-2005 Brand Name :
PDUFA Date : Estab. Name: TERBINAFINE HYDROCHLORIDE
Action Goal : Generic Name:
District Goal: 03-DEC-2005 Dosage Form: (CREAM)
Strength : 10 MG/G (1%)

FDA Contacts: B. DANSO Project Manager (HFD-617) 301-827-5849
A. MUELLER Team Leader (HFD-623) 301-827-5848

Overall Recommendation: ACCEPTABLE on 28-FEB-2005 by S. ADAMS (HFD-322) 301-827-9051

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Establishment : CFN : FEI :

(b) (4)

DMF No:

(b) (4)

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-FEB-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : (b) (4) FEI : (b) (4)
v [REDACTED] (b) (4)
DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-FEB-05
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : (b) (4) FEI : (b) (4)
v [REDACTED] (b) (4)
DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-FEB-05
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

DMF No:

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Responsibilities: DRUG SUBSTANCE MANUFACTURER

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Reason : DISTRICT RECOMMENDATION
