CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-387

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : April 8, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 08-APR-2002

SUBJECT: Examination of the Clinical endpoint study submitted with an ANDA for Clotrimazole Lozenge USP, 10 mg (Troche) to determine if the application is substantially complete for filing.

Roxane Laboratories Inc. has submitted ANDA 76-387 for Clotrimazole Lozenge USP, 10 mg (Troche). It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the Clinical endpoint study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the Clinical endpoint study submitted by Roxane on March 28, 2002 for its Clotrimazole product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements 4/11/2002

_____ Study does **NOT** meet statutory requirements

Reason:

N/A Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason:

Director, Division of Bioequivalence

4/12/02
Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 76-387 DRUG NAME Clotrimazole FIRM Roxane Labs

DOSAGE FORM(s) Troche (10mg)

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				
Assay Methodology	N/A				clinical end point Study
Procedure SOP					
Methods Validation					
Study Results ~~LnMin~~	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data		✓			Disintegration test submitted as requested
Pre-screening of patients	✓				
Chromatograms	N/A				
Consent forms	✓				
Composition	✓				
Summary of study	✓				
Individual Data & Graphs, Linear & Ln	✓				Individual Clinical Data
~~PK/P~~D data disk	✓				
Randomization Schedule	✓				
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				
Analytical site	N/A				
Study investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory *		✓			
BIO Batch Size	✓				
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture	✓				
Exp. Date RLD	✓				
Biostudy lot numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				
Waiver requests for other strengths / supporting data	N/A				

Additional comments: * Test Article Inventory was NOT found.

Recommendation: COMPLETE / INCOMPLETE 4/11/2002

Reviewed by Hoainhon Nguyen

_____ Date _____

Revised 6/7/2000

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM
FDA/CDER/ODEIV/DSPIDP/HFD-590

DATE: June 20, 2003

TO: ANDA 76-387 Protocol CLO-0199
Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

FROM: Eileen E. Navarro MD
Medical Officer, HFD-590

THROUGH: Steve Gitterman MD 6/29/03
Deputy Division Director and Acting Medical Team Leader, HFD-590

SUBJECT: Response to request for consultation regarding "clinical endpoints in a bioequivalence study for generic clotrimazole in the management of oropharygeal candidiasis". The sponsor submitted the original protocol CLO-0199 on January 6, 2000 for a bioequivalence study with clinical endpoints, comparing their Clotrimazole Troche, 10 mg, and Mycelex^{R} Troche, 10 mg. The study report was submitted to the Office of Generic Drugs, on 3/28/02. The consult was received at DSPIDP on June 19, 2003.

BACKGROUND:
Roxane Laboratories conducted a bioequivalence study with clinical endpoints to compare their generic Clotrimazole Troche, 10 mg with Mycelex® Troche, 10 mg. The primary protocol defined endpoint is clinical cure at day 21 (7 days after the end of treatment). However, in the sponsor's analysis, all patients with a positive culture at day 15 (1 day after the end of treatment), were discontinued regardless of clinical outcome at that time, and analyzed as treatment failures in the per protocol population.
In their review of the study report[1], OGD concludes that they are unable to justify the sponsor's designation of all patients with positive cultures at end of treatment as clinical failures. Further they are concerned that the exclusion of the above-mentioned patients from the evaluable population will result in an evaluable per-protocol population that is too small to meet statistical limits of equivalence for the 90% confidence interval of the proportional difference in cure rates.
Mycologic eradication of Candida in oropharyngeal candidiasis is difficult to accomplish, particularly in patients with severe infection, frequent recurrences, are highly immunosuppressed or infected with certain species of Candida[2], [3]. Furthermore, it is recognized that in these patients, clinical improvement occurs despite microbiologic persistence. Systemic antifungals approved for OPC and widely used for treatment o this entity (see Table below) have shown disparate outcomes for the clinical and microbiologic endpoints, based on baseline population characteristics described above[4].

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[1] Review of ANDA 76, 387 by Carol Y. Kim, Pharm.D., Office of Generic Drugs, January 31, 2003
[2] Rex JH, Walsh TJ, et al. Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America.Clin Infect Dis. 2000 Apr;30(4):662-78
[3] Walmsley, S, et al. "Oropharyngeal candidiasis in patients with human immunodeficiency virus: correlation of clinical outcome with in vitro resistance, serum azole levels and immunosuppression." CID. 32 (2001): 1554-61.
[4]Medical Officer's Review of NDA 19, 949.

Clinical and Mycological Efficacy of Fluconazole in OPC[4]				
Protocol	056-155		056-171	
Design	R, 3rd party blind		R, 3rd party blind	
Dosing Regimen	100 mg X 7 days		100 mg X 14 days	
Comparator	50 mg X 14 days		50 mg X 14 days	
Population	cancer, US		HIV, US	
Endpoints	**Clinical** 7days post treatment fluconazole end of treatment clotrimazole **Mycological** end of treatment (exclude patients with no cultures)		**Clinical** end of treatment for fluconazole and clotrimazole **Mycological** end of treatment (exclude patients with no cultures)	
Additional analyses	2,4 week post RX evaluations			
Efficacy : Clinical	Fluconazole	Clotrimazole	Fluconazole	Clotrimazole
Cure	28/38 73%	8/17 47%	26/27 96%	25/28 89%
Improved	6/38 16%	6/17 35%	1/27 4%	0
Total Success	**34/38 89%**	**14/17 82%**	**27/27 100%**	**25/28 89%**
Difference (95% CI)	7.12 (-17.72, 31.96)		10.71 (-4.38, 25.81)	
Efficacy : Mycological				
Eradication	**10/33 30%**	**2/18 11%**	**20/26 77%**	**7/24 29%**
Persistence	23/33 70%	16/18 89%	6/26 23%	17/24 71%
Difference (95% CI)	19.19 (-6.47. 44.85)		47.76 (19.40, 76.11)	
Relapse : 2 weeks	4/22 18%	3/7 43%	4/21 19%	9/15 60%
4 weeks	4/15 26%	1/5 20%	5/16 31%	4/8 50%

CONCLUSIONS:

The concern raised by the Office of Generic Drugs regarding the primacy of clinical endpoints in the evaluation of treatment efficacy in oropharyngeal candidiasis is well founded. The natural history of oropharyngeal candidiasis and current standards of medical practice for oropharyngeal candidiasis[5] support this view. DSPIDP agrees with the position taken by OGD regarding the importance of clinical outcomes over microbiologic efficacy for this indication, a concept also advanced in a draft guidance to industry on the development of agents for the indication of oropharyhgeal candidiasis[6]. The draft guidance lists Clinical Cure as the primary efficacy variable and provides consistency and support for this position. We concur with the Office of Generic Drug's analysis plan of including patients in the evaluable analysis if they have a clinical evaluation at the 7-day post therapy endpoint even if they had positive cultures at the end of therapy evaluation. Further we concur that patients discontinued as early clinical treatment failures be retained as failures for the primary efficacy analysis at the day 7 post therapy timepoint.

Eileen Navarro, MD,
Medical Officer

concurrence :
Steve Gitterman, MD,
HFD-590Deputy Division Director and Acting MTL

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[6] "Proposed Guidance for Industry: Developing Antifungals for Treatment of Oropharyngeal Candidiasis"

#466

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION
AND RESEARCH

DATE: July 10, 2003

FROM: John V. Kelsey, D.D.S., M.B.A. JVK 7/11/03
Dental Team Leader, Division of Dermatologic and Dental Drug Products (HFD-540)

THROUGH: Jonathan Wilkin, M.D. 7/18/03
Director, Division of Dermatologic and Dental Drug Products (HFD-540)

SUBJECT: Consult Request re: Endpoint for Bioequivalence Study of Clotrimazole Troches

TO: Dena R. Hixon, M.D., Associate Director of Medical Affairs
Office of Generic Drugs (HFD-600)

This consult includes a DRAFT OGD review of a bioequivalence study with a clinical endpoint and asks for comment on the appropriate management of patients with positive fungal cultures at the end of treatment. The requestor notes that a similar consult has been sent to the Division of Special Pathogens and Immune Drug Products (HFD-590).

Background:

A generic sponsor, Roxanne Laboratories, would like to market a Clotrimazole Troche, 10 mg. Using Mycelex® Troche, 10 mg. as the reference listed drug product. Because these are topical dosage forms, bioequivalence cannot be demonstrated using pharmacokinetic data, but has to be demonstrated by a clincial comparative efficacy study. The per protocol population is used for the evaluation of bioequivalence.

The Agency met with the Sponsor several times in 2000 and, among other things, agreed that the primary endpoint for their study should be the clinical outcome at approximately seven days post therapy. The Sponsor has conducted their study and has submitted it to OGD for review.

Consult Question (verbatim from consult):

In the Sponsor's final protocol, the primary endpoint is clinical cure at Day 21 (7 days after the end of treatment), as recommended. However, all patients with a positive

culture at Day 15 (one day following treatment) were discontinued, regardless of clinical outcome at that time, and they were analyzed as treatment failures in the per protocol population.

Based on previous discussions between OGD and the review divisions, it appears that the standard of care for immunocompromised patients with oropharyngeal candidiasis does not mandate that patients who are clinically cured but have positive cultures receive further therapy. Therefore the recommended primary endpoint was designated as clinical cure and fungal eradication was designated as a secondary endpoint.

In light of the designated primary endpoint of clinical cure at the 7-day follow-up visit, the sponsor's rationale for discontinuing patients with a positive fungal culture at end of treatment without regard to clinical status is not clear. Since a large proportion of those patients were noted to be clinically cured at the end of treatment, it is possible that many of them would have continued to be clinical cures at the 7-day follow-up visit. Therefore, it does not seem appropriate to designate them as failures in the final analysis. We plan to evaluate all patients that have data available for the 7-day follow-up visit according to the results at that time. Patients that were discontinued at end of treatment with both clinical and mycological failures will be carried forward as failures. All patients that show clinical improvement or cure at the end of treatment despite positive cultures will be excluded from the per protocol population if there is no data available at the 7-day follow-up.

It is likely that exclusion of the above-mentioned patients from the evaluable population will result in an evaluable per-protocol population that is too small to meet the established bioequivalence limits (-0.20, +0.20) for the 90% confidence interval of the proportional difference in cure rates. However, we are unable to justify the sponsor's designation of all patients with positive cultures at end ot treatment as clinical failures.

We would appreciate your comments on this aspect of study design."

Reviewer's Comment: HFD-540 holds NDA 18-713, Mycelex for oropharyngeal candidiasis, though that NDA was approved in 1983. Since that time the oropharyngeal candidiasis indication has been largely handled by HFD-590 or its predecessors that have regulated products for patients with HIV/AIDS. As a result, HFD-540 has no recent experience in regulating products for oropharyngeal candidiasis and defers on this matter to HFD-590, which has also received this consult. I have attached a copy of the consult provided by Eileen Navarro, M.D. of HFD-590.

ANDA 76-387
Drug Product: Clotrimazole Troche, 10 mg
Sponsor: Roxane Laboratories, Inc.
Reference Listed Drug: Mycelex® Troche/Lozenge (Bayer), NDA 18713
Submission date: March 28, 2002
V:/firmsnz/roxane/ltrs&rev/76387st.doc

Reviewer: Huaixiang Li, Ph.D., QMRS/OB/CDER
Requestor: Dena Hixon, MD, Carol Kim, Pharm.D., OGD/CDER, 8/26/2003

Objectives of the study

The primary objective of the study was to establish the bioequivalence of the test product, Roxane Laboratories, Inc., Clotrimazole Troche, 10 mg, and the reference product, Bayer, Mycelex® (Clotrimazole) Troche, 10mg, for the local treatment of oropharyngeal candidiasis in patients with Human Immunodeficiency Virus (HIV) infection, following application five times a day for 14 days.

Remarks

The sponsor submitted SAS datasets and programs to the Electronic Document Room (EDR), CDER on July 17, 2003. However, the datasets were not in SAS system XPORT transport format (Version 5 SAS transport file) and were not accepted by EDR. The datasets were resubmitted on September 16, 2003, following a telephone conversation with FDA medical and statistical reviewers and a telefax request sent to the sponsor.

The statistical analyses used information from three datasets: pat_sum, base_oro, and vis_data.

The following adjustments to these submitted datasets were made in accordance with recommendations of OGD medical reviewers.[1]

Exclusion/inclusion from FDA's intent-to-treat (ITT)/Per protocol (PP) populations

1) Twenty-five patients were excluded from the FDA's intent-to-treat (ITT) population since the sponsor inappropriately included all patients in their ITT population in the datasets.

2) Patient #102-1007 in the Roxane (Test product) treatment group was included in the FDA's Per Protocol (PP) population and the clinical response was changed from 'Cure' to 'Unevaluable' at the day 15 visit.

3) Eight patients: #104-1016, 112-1006, 113-1004[2], and 113-1008 in the Roxane treatment group, #101-1030, 107-1007, 107-1038, and 112-1002 in the Mycelex

[1] Please see the details in the FDA medical reviewer's report and summary table on page 5 of this report.

3) Eight patients: #104-1016, 112-1006, 113-1004[2], and 113-1008 in the Roxane treatment group, #101-1030, 107-1007, 107-1038, and 112-1002 in the Mycelex (Reference Listed Drug product) treatment group, were excluded from the FDA's PP population.

4) Based upon the Division of Scientific Investigations (DSI) inspection report, the fungal culture was changed from 'Negative' to 'Candida' for patient # 101-1002 at the Day 15 visit and for patient # 101-1024 at the Day 21 visit. These two patients were in the Roxane treatment group and were included in the sponsor's and FDA's PP populations.

Re-evaluation of clinical response at Day 21 visit for early discontinued patients in the PP population

The FDA Medical reviewer had the following comment: *"The sponsor's primary endpoint is defined as clinical response (complete disappearance of all oral lesions and all symptoms) at Day 21. Prior to completion of Day 21 evaluation, the following patients were discontinued by the sponsor per protocol: 1) patient with positive fungal culture of oropharynx on Day 15 and 2) patient not improved or worsened at Day 8 based on the clinical evaluation. Since deferring the appropriate treatment of HIV patients with clinical signs and symptoms of oral candidiasis is not advised due to the progression of their disease, it is appropriate to carry forward patients that were not improved at Day 8 as treatment failures in the PP population analysis. However, it is unclear why the sponsor discontinued patients with a positive fungal culture but absent clinical signs and symptoms at Day 15. Standard of care does not include further treatment in the absence of clinical evidence of disease unlike "requiring systemic antifungal therapy" as suggested in the sponsor's protocol. Therefore, such patients should not be considered treatment failures, as they might have continued to be clinically cured at Day 21 if observation had been continued (page 6 in Medical review report)."*

The medical reviewers explored the outcomes from patients with/without discontinuations. On June 19, 2003, the OGD medical reviewers consulted the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) and received a memorandum on June 20, 2003 about the appropriate evaluation of treatment efficacy in oropharyngeal candidiasis. In accordance with the concurred position with DSPIDP, the OGD medical reviewer pointed out: *"Therefore, those patients with both clinical failure (new or worsened signs and symptoms) and positive cultures at Day 15 should be carried forward as failures. Those with clinical cure (including improved) and positive cultures at Day 15 with no data at Day 21 should be excluded from the evaluable population for the Day 21 primary endpoints but should be analyzed according to the Day 15 evaluation for the secondary endpoints at Day 15 (page 14 in Medical review report)."*

Fifty-three (53) patients in the FDA's PP population were discontinued from the study before the Day 21 visit. Forty-two (42) patients were changed from "Failure" to "Unevaluable" and excluded from clinical response analysis at the Day 21 visit. Eleven

[2] Patient #113-1004 was inappropriately included in the sponsor's ITT and PP populations.

(11) patients were carried forward as "Failure" for the clinical response at the Day 21 visit. The table below shows these patients.

Site	Changed from 'Failure' to 'Unevaluable'		Carried forward as 'Failure'	
	Roxane	Myselex	Roxane	Myselex
101	1001, 1005, 1008, 1016, 1023, 1027	1017, 1028	1007	
102	1012, 1014	1008	1006, 1010	1013
103	1003, 1005, 1011, 1013, 1016	1010, 1017		
104	1001,1013, 1015, 1020,	1007, 1010, 1014, 1017, 1019	1022	1002, 1004, 1008, 1009
107	1026	1011, 1013, 1018, 1041	1012	
110	1012		1003	
111	1010	1004, 1005		
112		1004		
113		1002, 1003, 1007, 1009, 1010		
Total	20	22	6	5

Study Design

This was a multi-center, 2 arm parallel, investigator-blind study without the placebo/vehicle – control arm for HIV positive patients with oropharyngeal candidiasis that had been diagnosed by clinical examination and confirmed by fungal culture test.

After completion of the screening procedure, 189 patients were enrolled and randomly assigned to two treatment groups in the study. Each patient was instructed to apply the troches five times a day for 14 days. At the enrollment visit (Day 0 visit), the seven signs/symptoms, erythematous areas, white patches, mouth pain, altered taste, pruritus, dysphagia, and odynophagia ('Present', 'Absent'), were assigned to each patient. The fungal culture of oropharynx ('Candida', 'Negative', 'Other') was performed to confirm fungal diagnosis. The signs/symptoms scoring was performed at the Day 8 (±1 day - evaluation) visit. The signs/symptoms scoring and fungal evaluation were performed at the Day 15 (±1 day – end of treatment) visit and at the Day 21 (±1 day – follow-up) visit.

Outcome Variables

The FDA medical officer defined the primary endpoint to be clinical cure rate for clinical response at the Day 21 visit. The secondary endpoints were the clinical cure rate at the Day 15 visit and fungal culture negative rate at the Day 15 and Day 21 visits.[3]

Clinical cure at the Day 15 and 21 visits was defined as "complete disappearance of all oral lesions and all symptoms originally attributed to the diagnosis of oral candidiasis", regardless of the result of fungal culture of oropharynx. Clinical cure was satisfied to be absence for each of the seven signs/symptoms.

Statistical Analysis Methods

Equivalence Analysis

[3] Patients with Unevaluable or missing values for clinical response/fungal culture at Day 15/21 visit were excluded from the statistical analysis at Day 15/21 visit.

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 test and reference treatment should be contained within -.20 to .20 in order to establish equivalence.

The compound hypothesis to be tested is:

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

or $p_T - p_R \geq .20$

versus

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

where p_T = 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

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

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

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

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

We reject H_0 if $L \geq -.20$ 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 defined in the FDA medical reviewer's report:

Intent-to-treat population (ITT) – All subjects randomized to treatment and treated, with at least one post-baseline visit and positive baseline culture confirmed.

Per Protocol population (PP) – All subjects in the ITT population who completed the study and were evaluable for the analyses based on the protocol and FDA medical reviewer's best judgement.

According to the FDA medical reviewers, the determination of clinical equivalence of the two active treatments was to be assessed using the Per Protocol population (PP).

Statistical Analysis Results

A total of 189 patients were enrolled. The ITT population included 164 patients. The PP included 135 patients at the Day 15 visit and 94 patients at the Day 21 visit.

The following table shows the number of patients in each population per treatment arm*

Population /reason for exclusion	Roxane		Myselex		Total
Enrolled		**95**		**94**	**189**
Not treated	104-1005	1	110-1001	1	2
No post-baseline visit data	101-1009	1	101-1015	1	2
Safety population		**93**		**92**	**185**
Death: no post baseline visit	*113-1004*	1			1
Not randomized			*108-9999*	1	1
Baseline fungal culture negative	*101-1012, 101-1019, 103-1007, 107-1032, 107-1037*	5	*101-1014, 101-1025, 102-1011, 105-1004, 107-1042*	5	10
Baseline fungal culture not done	*108-1004, 108-1005, 108-1008, 110-1002*	4	*108-1003, 108-1006, 108-1007, 108-1009, 108-1010*	5	9
Intent-to-treat population		**83**		**81**	**164**
Death	*104-1016, 112-1006*	2	*107-1007*	1	3
Lost to follow-up	101-1018, 101-1031, 101-1032, 103-1012, 103-1015, 107-1021, 110-1004	7	101-1022, 107-1006, 110-1005, 110-1011	4	11
Non-compliance (visit window +3 day on Day 8 visit and subsequently discontinued by the sponsor)	110-1006	1			1
Removed from study in error	107-1028	1	107-1030	1	2
Patient did not return for personal reason	101-1021, 112-1012	2	101-1006, 101-1029, 111-1001	3	5
Schedule error			101-1003	1	1
Protocol violation			107-1035, *107-1038*	2	2
Adverse event	*113-1008*	1	*101-1030, 112-1002*	2	3
Per protocol population		**69**		**67**	**136**

*: The patient numbers in italics were inappropriately included in the sponsor's ITT population. The patient numbers in italics and underlined were inappropriately included in the sponsor's PP population.

Demographics and baseline

The means and ranges of age were 33.6 (19-53) years old for the test group and 34.7 (18-56) years old for the reference group in the PP population. The table below shows the sex and race distribution in the PP population. The sex and race of patients were comparably distributed among the two treatment groups for the PP populations, based on chi-square tests.

	Roxane	Myselex	Total
Sex			
Female	37	45	82
Male	32	22	54
Race			
Black	56	58	114
Caucasian	10	8	18
Mixed race	3	1	4

An analysis of the frequencies and chi-square tests for homogeneity of signs/symptoms for the PP populations at the enrollment visit was performed. There were no significant differences between treatment arms for six signs/symptoms except pruritus (p=0.031) at the enrollment visit.

Equivalence Analyses

We analyzed the data for equivalence for the clinical cure rate and fungal culture negative rate for the PP population at the Day 15 and 21 visits.

Summary of equivalence analyses

visit	Test* % cure or negative culture (No. of cure/negative /total number)	Reference* % cure or negative culture (No. of cure/negative /total number)	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
Clinical cure				
Day 21	**71.4 (35/49)**	**75.6 (34/45)**	**-21.2, 13.0**	**No**
Day 15	73.5 (50/68)	85.1 (57/67)	-24.4, 1.3	No
Fungal culture negative				
Day 21	67.4 (29/43)	48.7 (19/39)	-1.4, 38.8	No
Day 15	58.2 (39/67)	53.7 (36/67)	-11.1, 20.1	No

*: The rate of cure or negative culture equals the number of cure/negative divided by the total number, then multiplied by 100.

Primary endpoint: Clinical cure rate at Day 21 visit.

Equivalence has not been shown for the clinical cure rate at Day 21 visit for the PP population.

Secondary endpoints: Clinical cure rate at Day 15 visit and fungal culture negative rate at Day 15 and 21 visits.

Equivalence has not been shown for clinical cure rate at Day 15 visit and fungal culture negative rate at Day 15 and 21 visits for the PP population.

Comments on the Sponsor's Analysis

The results from the datasets were performed using the sponsor's PP population and endpoints without adjustment (see Remarks, page 1-3 of this review.) The missing or

unevaluable endpoint was treated as failure for clinical response or non-negative for fungal culture response. There were slight differences for clinical cure rate between the sponsor's reported results and results from the datasets submitted by the sponsor. The differences between our results and the results from the datasets were caused by the adjustment to the datasets in accordance with recommendations of OGD medical reviewers. The table below summarizes the results from the sponsor's report and those obtained from our analysis of the datasets submitted by the sponsor.

visit	Test % cure or negative culture (No. of cure/negative /total number)	Reference % cure or negative culture (No. of cure/negative /total number)	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
Sponsor's result*				
Clinical cure				
Day 21	47.2 (34/72)	45.1 (32/71)	-11.6, 15.9*	Yes
Day 15	70.8 (51/72)	80.3 (57/71)	-21.2, 2.3*	No
Fungal culture negative				
Day 21	41.7 (30/72)	28.2 (20/71)	0.5, 26.5*	No
Day 15	56.9 (41/72)	52.1 (37/71)	-8.9, 18.5*	Yes
Result from datasets				
Clinical cure				
Day 21	47.2 (34/72)	*49.3 (35/71)#*	-17.2, 13.1	Yes
Day 15	70.8 (51/72)	*81.7 (58/71)#*	-23.9, 2.1	No
Fungal culture negative				
Day 21	41.7 (30/72)	28.2 (20/71)	-0.9, 27.9	No
Day 15	56.9 (41/72)	52.1 (37/71)	-10.3, 19.9	Yes

*: The 90% confidence intervals in the sponsor's results were obtained without using Yates' correction.
#: The clinical cure rates were slightly different from these in the sponsor's results.

Safety

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

Conclusion

Primary endpoint: Equivalence has not been shown for the clinical cure rate at the Day 21 visit for the PP population.

Secondary endpoint: Equivalence has not been shown for Clinical cure rate at the Day 15 visit and fungal culture negative rate at the Day 15 and 21 visits for the PP population.

Huaixiang Li 12/3/03

Huaixiang Li, Ph.D.
Mathematical Statistician, QMR

Donald J. Schuirmann 11/26/03

Donald J. Schuirmann
Expert Mathematical Statistician, QMR

Stella G. Machado 11/30/03

Stella G. Machado, Ph.D.
Director, QMR

cc:
HFD-600 Dena R Hixon, Carol Y Kim, Krista Scardina
HFD-705 Stella G. Machado, Donald J. Schuirmann, Huaixiang Li
HFD-705 QMR Chron

RECORD OF TELEPHONE CONVERSATION

Agency: For your DS spec, particularly the particle size, how do you measure it? Did you measure it yourself? You need to confirm that you verify that the data from your vendor is adequate.

Firm: We used you just transfer data from our vendor to our COA, but I believe that we now verify the data. I will check and get back to you.

Continuation of call 1 hour later

Firm: Since this is such an old application, we did not verify the data on the batches we made. We could provide a commitment to test the API source on future lots.

Agency: Agreed, you need to commit to:
-Development of methods to verify the particle size
-Setting the limits and specifications
-Verify the API source and revise your COA
-You need to submit as a CBE 0 or 30 (look at the classifications) within 30 days post approval

Firm: Agreed, we will send in the commitment today.

DATE
7/13/04

ANDA NUMBER
76-387

IND NUMBER

TELECON

INITIATED BY

SPONSOR

FDA x

PRODUCT NAME
Clotrimazole Troche

FIRM NAME
Roxane

NAME OF PERSON WITH WHOM CONVERSATION WAS HELD
Elizabeth Ernst

TELEPHONE NUMBER
(614) 272-4785

SIGNATURE
P. Schwartz PJ 7/14/04
J. Fan 7/14/04
A. Vu 7/14/04

CC: 76-387
Chem Div I, T-con Notebook
V:\FIRMSNZ\ROXANE\TELECONS\76387.13july2004.doc

RECORD OF TELEPHONE CONVERSATION

Agency: [redacted] is a process impurity, which is limited at NMT [redacted] % in the drug substance, and is not expected to grow at product release or stability. In deed your stability data shows that. Hence you may limit it at NMT [redacted] % or drop the criterion. Also ship us samples of blister card and one HDPE bottle with drug samples.

Elizabeth Ernst: She will revise the release and stability criteria to drop related compound B since it is not growing and is a process impurity. She is sending samples by ~~FDE~~-EX.

FDA-

DATE	7/23/04
ANDA NUMBER	76-387
IND NUMBER	
TELECON	
INITIATED BY	
SPONSOR	FDA x
PRODUCT NAME	Clotrimazole Troche
FIRM NAME	Roxane
NAME OF PERSON WITH WHOM CONVERSATION WAS HELD	Elizabeth Ernst
TELEPHONE NUMBER	(614) 272-4785
SIGNATURE	R. Rajagopalan

CC: 76-387

7/23/04

V:\FIRMSNZ\ROXANE\TELECONS\76387.23july2004.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-387

CORRESPONDENCE

Boehringer Ingelheim
Roxane Laboratories

505(j)(2)(A) OK
28-MAY-2002

March 28, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Abbreviated New Drug Application
Clotrimazole Troche, 10 mg

Elizabeth A. Ernst, R.N., B.S.N.
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

Dear Madam/Sir:

In accordance with 21 CFR 314.94, Roxane Laboratories, Inc. is submitting an Abbreviated New Drug Application (ANDA) for Clotrimazole Troche, 10 mg. This ANDA consists of 15 volumes. This ANDA was formatted in accordance with the Guidance for Industry, Organization of an ANDA, February 1999.

The reference listed drug is MYCELEX® (clotrimazole) Troche, 10 mg, manufactured by Bayer Inc. The active ingredient is clotrimazole.

Four complete copies of the draft labeling are contained in the Archival and CMC Review copies of this application. The drug product will be manufactured, tested, labeled, packaged and released by Roxane Laboratories, Inc. No contract manufacturers or packagers are used for the proposed drug product. Clinical endpoint study reports are also included in this application.

Samples and the methods validation package will be submitted upon the request and direction of the Office of Generic Drugs. Roxane Laboratories, Inc. commits to providing full cooperation to resolve any problems that may arise during the methods validation testing as part of the "Post-Approval" for the above listed drug product.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Mr. Steven Eastham, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Rebecca Braatz, Regulatory Affairs Associate, at (614) 272-4709.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

APPEARS THIS WAY
ON ORIGINAL

Boehringer Ingelheim
Roxane Laboratories

76-387

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

Attention: Paras Patel

May 20, 2002

Abbreviated New Drug Application
Clotrimazole Troche, 10 mg
Amendment – Response to FDA Request

Elizabeth A. Ernst, R.N., B.S.N.
Associate Director, Regulatory Affairs, DRA-Multisource Products for Roxane Laboratories, Inc.

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Mr. Patel:

We wish to amend our ANDA for Clotrimazole Troche, 10 mg. In reference to your telephone call of May 16, 2002, enclosed please find a side-by-side comparison of our Clotrimazole Troche blister carton with that of the brand product.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Rebecca Braatz, Regulatory Affairs Associate, at (614) 272-4709.

Respectfully,

Elizabeth A. Ernst, R.N., B.S.N.
Associate Director, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.

RECEIVED
MAY 2 2 2002
OGD / CDER

ANDA 76-387

MAY 28 2002

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
1809 Wilson Rd.
Columbus, OH 43228

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.

Reference is made to the telephone conversation dated May 16, 2002 and to your correspondence dated May 20, 2002.

NAME OF DRUG: Clotrimazole Lozenges USP, 10mg

DATE OF APPLICATION: March 28, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 29, 2002

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:

Sarah Ho
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

ANDA 76-387
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis,Chief, RSB GDavis 28-MAY-2002 date
HFD-615/PPatel,CSO _____ date
Word File V:\Firmsnz\ltrs&rev\Roxane\76387.ACK
F/T PMP 5/28/02
ANDA Acknowledgment Letter!

AUG 2 - 2002

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-387 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Clotrimazole Troche, 10 mg.

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1.

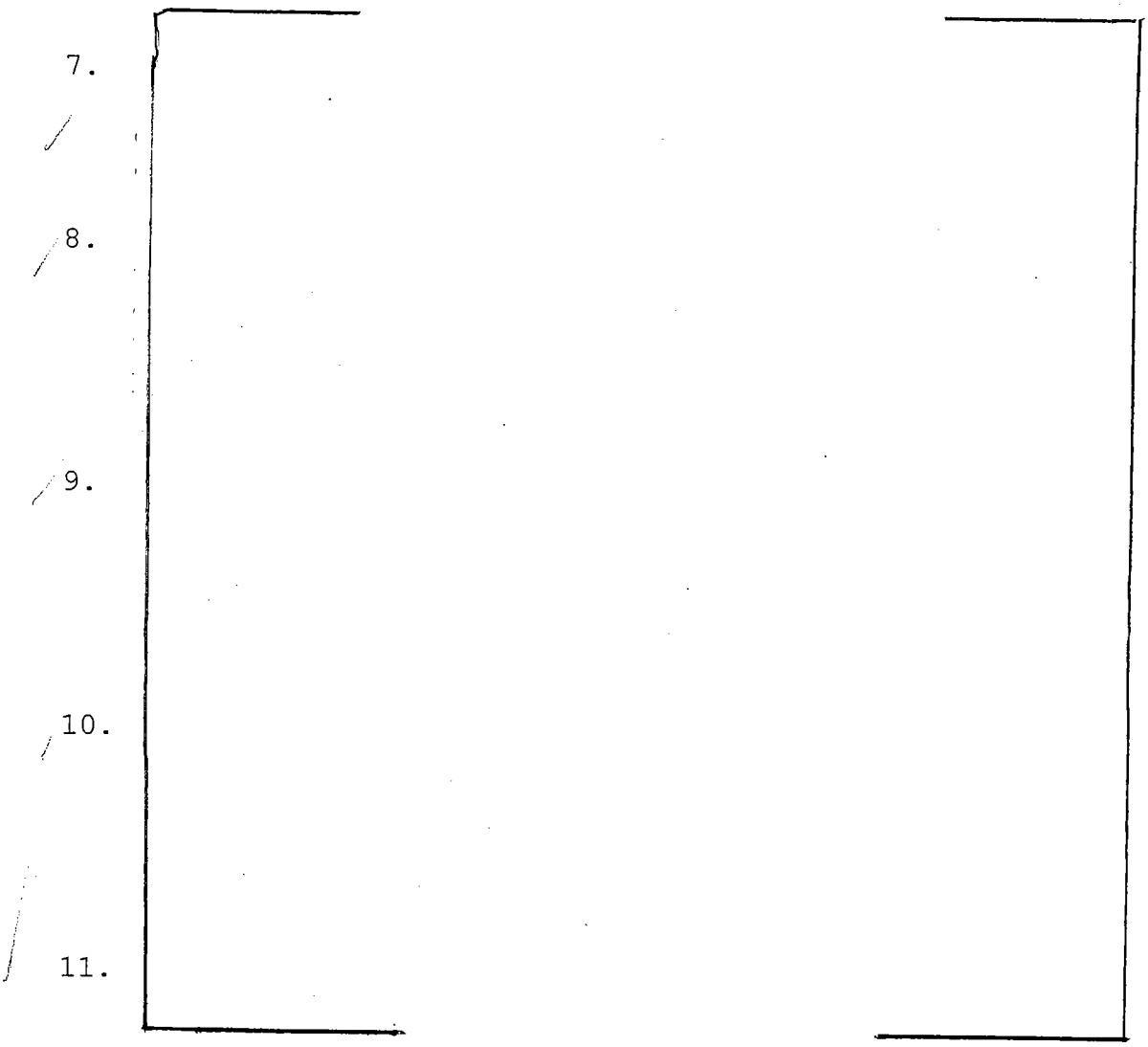
2.

3.

4.

5.

6.



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

1. Please provide all available room temperature stability data.

2. Bioequivalence and labeling information you have provided are pending review. After the reviews are completed, any deficiencies found will be communicated to you separately.

3. All facilities referenced in your ANDA should be in compliance with CGMP at the time of approval.

4. Since the drug product is not a USP product, your drug product analytical methods will be validated by a FDA district laboratory after all the specification related issues are satisfactorily resolved.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

Attention: Ms. Sarah Ho

ANDA 76-387
Clotrimazole Troche, 10 mg

MINOR AMENDMENT
Chemistry Deficiencies

Roxane Laboratories, Inc.

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products
Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com
P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

September 18, 2002

Dear Ms. Ho:

We wish to amend ANDA 76-387, Clotrimazole Troche, 10 mg. This is in response to the Minor Amendment Letter dated August 2, 2002, and faxed to us on August 5, 2002 (copy attached). Enclosed please find responses to the chemistry deficiencies and comments.

We have also submitted a copy of this amendment to Mr. Steven Eastham, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Paul Brusky, Regulatory Affairs Associate, at (614) 241-4132.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

RECEIVED
SEP 19 2002
OGD / CDER
9/19/02

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF
FPL

Attention: Sarah Ho

November 15, 2002

LABELING Amendment
ANDA 76-387
Clotrimazole Troche (Clotrimazole Lozenges), 10 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Ho:

In response to the labeling deficiency correspondence from Ms. Beverly Weitzman dated October 25, 2002 (copy attached), we wish to amend ANDA 76-387 for Clotrimazole Troche (Clotrimazole Lozenges), 10 mg. Enclosed please find twelve (12) copies of final printed labeling for this ANDA submission.

Please note that the name of our product has been changed from Clotrimazole Troche, 10 mg to Clotrimazole Troche (Clotrimazole Lozenges), 10 mg in accordance with our November 5, 2002 telephone conversation with Mr. John Grace, Branch Chief, Labeling, Office of Generic Drugs.

We have also submitted a copy of this amendment to Mr. Steven Eastham (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470.

Respectfully,

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

RECEIVED
NOV 18 2002
OGD / CDER

REVIEW OF PROFESSIONAL LABELING - #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76387

Date of Submission: March 28, 2002

Applicant's Name: Roxane Laboratories, Inc.

Established Name: Clotrimazole Lozenges, USP 10 mg

Labeling Deficiencies:

1. **GENERAL COMMENT**

   The established name for this product is "Clotrimazole Lozenges". Please revise your labels and labeling accordingly.

2. **CONTAINER** - 10 mg tablet (bottles of 70, 140, and 500)

   Refer to (1) general comment

3. **UNIT DOSE BLISTER CARTON** (7 x 10 unit dose tablets)

   - Revise the quantity statement "10x7 unit dose tablets" to read "7 x 10 unit dose tablets" (include spacing in between the "x"). Please note that the first number represents the number of strips and the second number represents the number of tablets.
   - Add the statement "For institutional use only".
   - Refer to (1) general comment

4. **BLISTER LABEL**

   Refer to (1) general comment

5. **INSERT**

   a. **GENERAL COMMENTS**

      i. Refer to (1) general comment

      ii. Please use the full establish name, "Clotrimazole Lozenges" in the following sections:

      - DESCRIPTION
      - INDICATION AND USAGE
      - CONTRAINDICATIONS
      - DOSAGE AND ADMINISTRATION
      - HOW SUPPLIED

b. HOW SUPPLIED

Please revise the description of the unit dose tablets to read "10 mg white tablets, 7 x 10 unit dose tablets" instead of " 10 mg white tablets, blister pack 10x7".

Please revise your labeling, as instructed above, and submit 12 final printed copies for approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug. We suggest that you routinely monitor the following

website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all the differences annotated and explained.

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

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
NTAF

December 30, 2002

Attention: Beverly Weitzman, PharmD

LABELING Amendment
ANDA 76-387
Clotrimazole Troche (clotrimazole lozenges)

Elizabeth A. Ernst
Associate Director, DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000

Dear Dr. Weitzman:

In response to your labeling deficiency correspondence dated December 18, 2002, we wish to amend ANDA 76-387 for Clotrimazole Troche (clotrimazole lozenges). Enclosed please find twelve (12) copies of final printed labeling for this ANDA submission.

We have also submitted a copy of this amendment to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470.

Respectfully,

Elizabeth A. Ernst
Associate Director, DRA-Multisource Products

RECEIVED
DEC 31 2002
OGD / CDER

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Sarah Ho

January 31, 2003

TELEPHONE Amendment
ANDA 76-387
Clotrimazole Troche (Clotrimazole Lozenges), 10 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Ho:

In response to our January 23, 2003 telephone conversation, we wish to amend ANDA 76-387 for Clotrimazole Troche (Clotrimazole Lozenges), 10 mg. Enclosed please find revised copies of our Drug Substance Specification and Drug Product Specification, with the changes we discussed.

Drug Substance Specification:
- Total known and unknown related substances increased from —% to —%
- Note included in ——— specification that this related substance is not included in the total known and unknowns

Drug Product Specification:
- Total known and unknown related substances increased from —% to —% for release
- Total known and unknown related substances increased from —% to —% for stability
- Single largest unknown specification is —% for both release and stability
- Roxane Laboratories commits to developing an HPLC method to monitor and set limit for ——— related substance in drug product

We have also submitted a copy of this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470.

Respectfully,

Elizabeth A. Ernst
Associate Director, DRA-Multisource Products

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N / AM

April 8, 2003

Attention: Sarah Ho

TELEPHONE Amendment
ANDA 76-387
Clotrimazole Troche, 10 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Ho:

In response to our telephone conference March 12, 2003, we wish to amend ANDA 76-387 for Clotrimazole Troche, 10 mg. Enclosed please find a revised drug product specification, containing methodology for the [redacted] assay; also enclosed is a validation report for this method.

We have also submitted a letter of notice for this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470.

Respectfully,

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

RECEIVED
APR 09 2003
OGD / CDER

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT
N/AG

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

July 17, 2003

Attention: Krista Scardina

Bioequivalency Amendment
ANDA 76-387
Clotrimazole Troche (Clotrimazole Lozenges), 10 mg

Dear Dr. Scardina:

In response to your telephone request, we wish to amend ANDA 76-387 for Clotrimazole Troche (Clotrimazole Lozenges), 10 mg. Enclosed please find electronic files for Clotrimazole Study CLO-0199: Final Report, SAS Programs, and Datasets.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470.

Respectfully,

Elizabeth A. Ernst
Associate Director, DRA-Multisource Products

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

N/AA

July 21, 2003

Attention: Sarah Ho

Gratuitous Amendment
ANDA 76-387
Clotrimazole Troche, 10 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Ho:

We wish to submit a Gratuitous Amendment for ANDA 76-387, Clotrimazole Troche, 10 mg. Enclosed please find a revised Roxane Laboratories' Drug Product Specification No. 1278-04. Details of revisions are as follows:

- [redacted] clarified
- Corrected [redacted]
- Added clarification regarding use of [redacted] assay
- Corrected [redacted]

We have also submitted a letter of notice for this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470.

Respectfully,

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

RECEIVED
JUL 22 2003
OGD/CDER

7-29-03

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT

N/A5

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Ruth Wazala

September 16, 2003

Bioequivalency Amendment
ANDA 76-387
Clotrimazole Troche (Clotrimazole Lozenges), 10 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Dr. Wazala:

In response to our telephone conversation with Carol Kim and Helen Lee, DBE, August 27, 2003; and the telefax received on that date (copy attached), we wish to amend ANDA 76-387 for Clotrimazole Troche (Clotrimazole Lozenges), 10 mg. Enclosed please find SAS Transport files for Clotrimazole Study CLO-0199.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470.

Respectfully,

Elizabeth A. Ernst
Associate Director, DRA-Multisource Products

cc: Carol Kim, Helen Lee

SEP 17 2003

MAR 06 2004

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:76-387 APPLICANT:Roxane Laboratories, Inc.

DRUG PRODUCT: Clotrimazole Troche, 10 mg

The Division of Bioequivalence has completed its review and the following deficiencies have been identified:

The data submitted to ANDA 76-387 failed to demonstrate bioequivalence of Roxane's Clotrimazole Troches, 10 mg, with the reference listed drug, Mycelex Troche/Lozenge®, using the accepted primary endpoint of clinical cure at 7-day post treatment (day 21).

1. The primary endpoint is a clinical cure defined as complete disappearance of all oral lesions and all symptoms originally attributed to the diagnosis of oral *candidiasis* at the 7-day follow-up visit (day 21). You inappropriately discontinued a large number of patients (43) at the end of treatment and designated them as failures in the PP analysis because of positive fungal cultures regardless of clinical status. Standard of care does not require further systemic treatment for positive fungal cultures in the absence of clinical evidence of disease. The Division of Special Pathogen and Immunologic Drug Products (DSPIDP/HFD-590) also concurred and supported the OGD's analysis plan placing emphasis on the importance of the clinical outcomes over fungal eradication for treatment of this indication.

2. The six patients with positive cultures but absent clinical signs and symptoms at day 15 who actually returned for the Day 21 evaluation were analyzed by FDA according to the Day 21 data. Half of them were clinically cured at day 21 and half of them were failures. The nine patients with both a positive fungal culture and clinical failure at the end of treatment were analyzed as clinical failures. All patients that had positive fungal cultures at day 15 despite clinical outcome of cure or "improved" at that time were considered as unevaluable and excluded from the evaluable population if Day 21 data were not available.

3. You also analyzed four patients that died during the study as treatment failures in your PP analysis. Since they were

discontinued for reasons unrelated to the study drug, they were excluded from the FDA's PP analysis and not analyzed as treatment failures.

4. One patient was not randomized but received the reference drug and completed the Day 8 visit prior to death unrelated to the study drug. This patient was included only in the safety population for the FDA analysis.

5. You excluded one patient that had a clinical response of cure on the Day 21 visit from the PP population analysis because the fungal culture was not performed on Day 15. Because the Day 15 fungal culture may have no impact on the primary endpoint, this patient was included in the FDA analysis of the primary endpoint as a cure but excluded from the Day 15 secondary endpoint of mycological response.

6. You analyzed three patients as treatment failures because they discontinued the study due to adverse events. Because these patients were not evaluated as treatment failures, they were excluded from the FDA's PP analysis.

7. One patient received prohibited medication (topical clotrimazole cream) during the study, and was therefore excluded from the FDA's PP analysis because of this protocol violation.

8. After further exclusion of unevaluable patients that you inappropriately designated as clinical failures, the 90% CI of the proportional difference between products in clinical cure rates in the evaluable population at the primary endpoint was (-21.2, +13.0), which failed to meet the accepted bioequivalence criteria. All secondary endpoints (clinical cure rate at the end of treatment, fungal culture results at the end of treatment and at 7-day follow-up visit) also failed to meet the bioequivalence limits, and therefore further support a conclusion that this study is not adequate to demonstrate bioequivalence of your product to the reference listed drug, Mycelex Troche/Lozenge®.

9. The Division of Scientific Investigation concluded that the inspected sites did not comply with the Final Rule for retention of BA and BE testing samples. The Final Rule requires that retention samples be randomly collected and retained from each shipment received by the clinical site. It is your responsibility to assure that the clinical sites

for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 210.38 and 320.63. If you fail to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

Sincerely yours,

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

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-387 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Clotrimazole Troche, 10 mg

The deficiency presented below represents a MAJOR deficiency.

A. Deficiency: JAN 2 1 2004

Bioequivalence deficiencies were communicated to you via facsimile on January 8, 2004. You should address the issues in the January 8, 2004 communication prior to or concurrent with your response to this communication.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 22 2004

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:76-387 APPLICANT:Roxane Laboratories, Inc.

DRUG PRODUCT: Clotrimazole Troche, 10 mg

The following comments have been re-written to facilitate your understanding of our review and the deficiencies that we identified.

The Division of Bioequivalence has completed its review and the following deficiencies have been identified:

The data submitted to ANDA 76-387 failed to demonstrate bioequivalence of Roxane's Clotrimazole Troches, 10 mg, with the reference listed drug, Mycelex Troche/Lozenge®.

1. The accepted primary endpoint for a bioequivalence study of clotrimazole troche is clinical cure at the follow-up visit 7 days after the end of a 14-day course of therapy (day 21). Clinical cure is defined as complete disappearance of all oral lesions and all symptoms originally attributed to the diagnosis of oral *candidiasis*. Culture results are not part of the determination of clinical cure.

   You discontinued 52 patients that had positive fungal cultures at the end of treatment and analyzed them as treatment failures without regard to their clinical status. Standard of care does not require that patients with persistent positive cultures receive further treatment in the absence of clinical signs and symptoms of oral candidiasis. Therefore, all patients who had a clinical evaluation of "cure" or "improved" at the end of treatment should have been continued in the study for 7 days of follow-up without further therapy and evaluated for clinical cure at the 7-day follow-up visit (day 21). Any patient who developed worsening signs and symptoms during that follow-up period should have been discontinued at the time of worsening, analyzed as a treatment failure, and provided with effective therapy. However, any patient who continued to show improvement or absence of symptoms should have continued in follow-up and returned for the 7-day follow-up visit for evaluation of the primary endpoint.

OGD has consulted the Division of Special Pathogen and Immunologic Drug Products (DSPIDP/HFD-590), and DSIDP confirmed our understanding of the standard of care and the appropriate endpoint for this study. The analysis for treatment of this indication should focus on the clinical outcome instead of fungal eradication.

2. The following is a description of how OGD analyzed the patients with positive fungal cultures that you analyzed as failures:

   a) Six patients with positive cultures and absent clinical signs and symptoms at day 15 actually returned for the Day 21 evaluation. We analyzed those 6 patients according to the Day 21 data. Half (3) of them (R#103-1001, R#103-1002, R#103-1004) were clinically cured at day 21 and the other half (3) of them (T#102-1003, T#113-1005, R#105-1003)were failures.

   b) Nine patients, 5 in the reference group (#102-1013, #104-1002, #104-1004, #104-1008, #104-1009) and 4 in the generic group (#102-1006, #102-1010, #104-1022, #107-1012), had both a positive fungal culture and clinical failure (no improvement in signs and symptoms of oral candidiasis) at the end of treatment. We agree that these 9 patients were appropriately analyzed as clinical failures.

   c) All other patients that had positive fungal cultures and clinical outcome of "cure" or "improved" at day 15 were discontinued from the study, and no follow-up data were available at day 21. We considered them as unevaluable and excluded them from the PP analysis. (Reference group #104-1007, #107-1013, #107-1041, #113-1010, 101-1017, 101-1028, 103-1010, 103-1017, 104-1010, 104-1014, 104-1017, 104-1019, 107-1011, 107-1018, 111-1004, 111-1005, 112-1004, 113-1002, 113-1003, 113-1007, 113-1009. Generic group #101-1027, #103-1011, #110-1003, #111-1010,#101-1001, 101-1005, 101-1008, 101-1016, 101-1023, 102-1008, 102-1012, 102-1014, 103-1003, 103-1005, 103-1013, 103-1016, 104-1001, 104-1013, 104-1015, 104-1020, 107-1026, 110-1012.)

3. You also analyzed four patients (#104-1016, #107-1007, #112-1006, #113-1004) that died during the study as treatment failures in your PP analysis. Since their deaths were unrelated to the study drug and no data was provided to suggest worsening of their clinical signs and symptoms of

oral candidiasis, they were excluded from our PP analysis and not analyzed as treatment failures.

4. One patient (#108-9999) was not randomized but received the reference drug and completed the Day 8 visit prior to death from bronchopneumonia, unrelated to the study drug. Because this patient was not randomized, he/she was excluded from both the PP and ITT population for our analysis.

5. You excluded from the PP population analysis one patient (#102-1007) that had a clinical response of "cure" on the Day 21 visit because the fungal culture was not performed on Day 15. Because the primary endpoint of clinical cure does not depend on culture results, we included this patient in our primary endpoint analysis as a cure but excluded him/her from the analysis of the Day 15 secondary endpoint of mycological response.

6. You analyzed three patients (#101-1030, #112-1002, #113-1008) as treatment failures because they discontinued the study due to adverse events. Because these patients did not have worsening signs and symptoms of oral candidiasis, they were excluded from our PP analysis.

7. One patient(#107-1038) received prohibited medication (topical clotrimazole cream) during the study, and was therefore excluded from our PP analysis as a protocol violation.

8. After excluding the unevaluable patients that you had inappropriately analyzed as clinical failures, the PP evaluation of the primary endpoint failed to meet the accepted bioequivalence criteria. The 90% CI of the proportional difference between clinical cure rates was (-21.2, +13.0).

   All secondary endpoints (clinical cure rate at the end of treatment, fungal culture results at the end of treatment, and fungal culture at 7-day follow-up visit) also failed to meet the bioequivalence limits. Therefore the secondary endpoints further support the conclusion that this study is not adequate to demonstrate bioequivalence of your product to the reference listed drug, Mycelex Troche/Lozenge®.

9. The following Statistical Analysis Method is recommended:

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in proportions between test and reference treatment should be contained within -.20 to .20 in order to establish equivalence.

The compound hypothesis to be tested is:

H0: $p_T - p_R \leq -.20$ or $p_T - p_R \geq .20$

versus

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

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

Let

n_T = sample size of test treatment

$c n_T$ = number of cure patient of test treatment

n_R = sample size of reference treatment

$c n_R$ = number of cure patient of reference treatment

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

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

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

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

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

We reject H0 if $L \geq -.20$ and $U \leq .20$

Rejection of the null hypothesis H0 supports the conclusion of equivalence of the two products.

10. The Division of Scientific Investigation concluded that the inspected sites did not comply with the Final Rule for retention of BA and BE testing samples. The Final Rule requires that retention samples be randomly collected and retained from each shipment received by the clinical site. It is your responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 210.38 and 320.63. If you fail to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

Sincerely yours,

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

CC: ANDA 76-387
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ C.Kim
HGD-600/ D. Hixon

V:\FIRMSnz\roxane\ltrs&rev\76387A.mor0302

Endorsements: (Final with Dates)
HFD-600/C. Kim
HFD-600/D. Hixon ORH 1/22/04
HFD-650/D. Conner NMZ 1/21/04

BIOEQUIVALENCY - UNACCEPTABLE

submission date:
March 28, 2002

1. Bioequivalence Study (STU)

Strengths: 10 mg
Outcome: UC

2. Study Amendments (STA)

Strengths: 10 mg
Outcome: N/A

July 17, 2003 (Electronic datasets)
September 16, 2003 (Electronic datasets)

Outcome Decisions: **AC** - Acceptable
WC - Without charge
IC - Incomplete
UC - Unacceptable
N/A- Not applicable

BIOEQUIVALENCY AMENDMENT

FEB 12 2004

ANDA 76-387

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)

APPLICANT: Roxane Laboratories, Inc.

TEL: 614 272-4785

ATTN: Elizabeth A. Ernst

FAX: 614 276-2470

FROM: Krista Scardina

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on March 28, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Clotrimazole Troche, 10 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all 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. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

FEB 12 2004

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:76-387 APPLICANT:Roxane Laboratories, Inc.

DRUG PRODUCT: Clotrimazole Troche, 10 mg

The Division of Bioequivalence has completed its review and the following deficiencies have been identified:

There is no USP or FDA dissolution method available for this product. A dissolution method should be developed for this product. Please refer to the Guidances for Industry: "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations" and "Dissolution Testing of Immediate Release Solid Oral Dosage Forms" for additional information regarding development of dissolution methods. The following information is generally recommended to be included in a dissolution method development report:

- The pH solubility profile of the drug substance
- Dissolution profiles generated at different agitation speeds (e.g., 100 to 150 revolutions per minute (rpm) for U.S. Pharmacopeia (USP) Apparatus I (basket), or 50 to 100 rpm for USP Apparatus II (paddle))
- Dissolution profiles generated on all strengths in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer). Water can be used as an additional medium. If the drug being considered is poorly soluble, appropriate concentrations of surfactants are recommended.

Sincerely yours,

Barbara M Davit

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

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Krista Scardina

February 17, 2004

N/A6

MAJOR Amendment
ANDA 76-387
Clotrimazole Troche, 10 mg

Dear Ms. Scardina:

We wish to amend ANDA 76-387 for Clotrimazole Troche, 10 mg. Enclosed please find a point-by-point response to the questions in the facsimile major deficiency letter dated January 22, 2004 (copy attached). As you may recall, Roxane requested clarification of an earlier deficiency letter sent by the agency on January 8, 2004.

Please note that Roxane Laboratories does not agree with the Agency's statement that the Roxane laboratories generic clotrimazole product is NOT bioequivalent to the Myclex® Troche. Roxane Laboratories has made several attempts to identify the evaluable population used by the agency for its per protocol (PP) evaluation of the primary endpoints. Despite our efforts, we have not been able to duplicate your results and confidence intervals.

Therefore, we have outlined our approach to identifying the evaluable population used by the agency for its PP evaluation based on the information provided in your letter dated January 22, 2004. In addition, we have also included a CD which contains the SAS code and data sets that we used to generate our confidence intervals for both the 97 patient and the 101 patient evaluable populations noted in our point-by-point response. This will allow the agency to duplicate these analyses.

Roxane laboratories is committed to working with the agency to resolve any and all issues regarding the analysis of this project. We would like to work closely with the Agency to resolve all issues as quickly as possible since we believe the product to be bioequivalent and thus would like to obtain approval as soon as possible.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Marilynn Davis, Clinical Research Manager, at (614) 241-4123.

Respectfully,
Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

5.1

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AC

Attention: Thuyanh (Ann) Vu

February 20, 2004

MAJOR Amendment
ANDA 76-387
Clotrimazole Troche, 10 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Vu:

In response to the CMC Major Deficiency Letter we received on January 21, 2004 (copy attached), we wish to amend ANDA 76-387 for Clotrimazole Troche, 10 mg. Please be advised that on February 17, 2004, we responded to this deficiency, and a copy of our cover letter from the response is attached.

We have also submitted a letter of notice for this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by fax at (614) 276-2470.

Respectfully,

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

RECEIVED
FEB 23 2004
OGD/CDER

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs – HFD 600
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, Room 150
Rockville, MD 20855 – 2773

NAE
3 March 2004

26 February, 2004

(NC)

Resubmission of Electronic Files Amendment
ANDA 76-387
Clotrimazole Troche, 10 mg

Dear CDER Electronic Document Room Staff;

We wish to amend ANDA 76-387 for Clotrimazole Troche, 10 mg. Enclosed please find a CD which contains the reformatted SAS code and data sets as requested in your facsimile dated 23 February, 2004 which was in response to our Major Amendment submitted 17 February, 2004. A copy of your facsimile is attached.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Marilynn Davis, Clinical Research Manager, at (614) 241-4123.

Respectfully,

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

61

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT
N/AB

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

March 10, 2004

Attention: Krista Scardina

Bioequivalency Amendment
ANDA 76-387
Clotrimazole Troche, 10 mg

Dear Dr. Scardina:

In response to your deficiency letter of February 12, 2004 (copy attached), we wish to amend ANDA 76-387 for Clotrimazole Troche, 10 mg. Enclosed please find a point-by-point response to this deficiency letter.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Rebecca Braatz, Regulatory Affairs Associate, at 614-272-4709.

Respectfully,

Elizabeth A. Ernst
Associate Director, DRA-Multisource Products

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Boehringer Ingelheim
Roxane Laboratories

N/AB

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

April 2, 2004

Attention: Aaron Sigler

Bioequivalency Amendment
ANDA 76-387
Clotrimazole Troche, 10 mg

Dear Mr. Sigler:

In response to your telephone deficiency of March 26, 2004, we wish to amend ANDA 76-387 for Clotrimazole Troche, 10 mg. Enclosed please find Roxane Laboratories' Certificates of Analysis containing the data requested in your telephone contact.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Rebecca Braatz, Regulatory Affairs Associate, at 614-272-4709.

Respectfully,

Rebecca Braatz

(Rebecca Braatz, Regulatory Affairs Associate, for)
Elizabeth A. Ernst
Associate Director, DRA-Multisource Products

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

APR 27 2004

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-387 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Clotrimazole Troche, 10 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet, and the following deficiency has been identified:

> The Division of Bioequivalence (DBE) does not agree with your proposed dissolution specification of "Not less than —% (Q) in 60 minutes". Please revise the dissolution testing specification for your product to the following specification:
>
> Not less than (NLT) —% (Q) of the labeled amount of clotrimazole in the dosage form is dissolved in 45 minutes.

Please acknowledge acceptance of the above dissolution specification of your product.

Sincerely yours,

for Barbara M. Davit

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

6.1

Boehringer Ingelheim
Roxane Laboratories

ORIGINAL

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

May 4, 2004

Attention: Aaron Sigler

Bioequivalency Amendment
ANDA 76-387
Clotrimazole Troche, 10 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Fax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Mr. Sigler:

In response to the Bioequivalency Deficiency Letter we received on April 27, 2004 (copy attached), we wish to amend ANDA 76-387 for Clotrimazole Troche, 10 mg. Please be advised that we have revised our drug product specification accordingly. A copy of the revised specification is enclosed.

We have also submitted a letter of notice for this amendment to Ms. Thuyanh (Ann) Vu, Office of Generic Drugs, and to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by fax at (614) 276-2470.

Respectfully,

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

RECEIVED
MAY 0 5 2004
OGD/CDER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

Date: 05 May 2004

To: Elizabeth Ernst

Phone: 6142724785

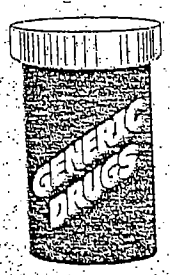
Fax: 6142762470

From: Krista Scardina

Phone: (301) 827-5845

Fax: (301) 594-0183

Number of Pages: 3
(Including Cover Sheet)



Comments:

This is for your information and the basis for accepting your bioequivalence study with clinical endpoints. No response is needed.

Thanks!
Krista

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-387 APPLICANT:Roxane Laboratories, Inc.

DRUG PRODUCT: Clotrimazole Troche, 10 mg

The Division of Bioequivalence has completed its review and the following comments have been identified:

With the additional data for four patients submitted to ANDA 76-387 Amendment dated February 17, 2004, the 90% CI of the difference in clinical cure rates between the test and reference products, using the accepted primary endpoint of a clinical cure at 7-day post treatment (day 21), is within the established limits of (-0.20, +0.20) and the study is therefore adequate to demonstrate bioequivalence of your Clotrimazole Troche to the reference listed drug, Mycelex Troche/Lozenge®, pending an acceptable response to deficiency comment regarding the dissolution method.

1. The OGD provided clear guidance to clarify that the acceptable primary endpoint for a bioequivalence study with clinical endpoints for this product is clinical response at the follow-up visit one week after the end of treatment and not fungal culture result. Fungal culture of the oropharynx does not always correlate with the clinical response. It is your responsibility to assure that the design of the study is appropriate to assure that the data provided will allow for accurate analysis of the primary endpoint.

2. Patients who fail to complete the final visit for reasons other than treatment failure (lost to follow-up, adverse event or death unrelated to treatment, or personal reasons) should be excluded from the evaluable population. These patients have missing efficacy variables for the primary endpoint and do not provide sufficient data to be considered as either a cure or a failure. Therefore, they should not be designated treatment failures. They should be considered as unevaluable and excluded from the evaluable population.

3. In the future, you are strongly advised to submit an amended protocol for review prior to conducting a bioequivalence study for an ANDA when your original protocol requires a significant change in study design based on the OGD recommended primary endpoint.

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

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-387 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Clotrimazole Troche, 10 mg

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

We acknowledge that you have accepted the following dissolution method and specification:

The dissolution testing should be conducted in 500 mL of 0.1N HCl at 37°C ± 0.5°C using USP Apparatus 2 (Paddles) at 50 rpm. The test product should meet the following specification:

> Not less than —% (Q) of the labeled amount of clotrimazole in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M Davit

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

7.1

ORIGINAL

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT
N/AA

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Thuyanh (Ann) Vu

June 24, 2004

Telephone Amendment
ANDA 76-387
Clotrimazole Troche, 10 mg

Dear Ms. Vu:

In response to your telephone call on June 22, 2004, we are submitting this telephone amendment for ANDA 76-387 for Clotrimazole Troche, 10 mg. In accordance with your request we have added to our product specification a second Identification Test (TLC as per current USP and Supplement) and disintegration testing (as per current USP and Supplement). The revised product specification is attached. We also enclose a revised Stability Commitment and Protocol which contains the required disintegration testing.

We have also submitted a copy of this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Rebecca Braatz, Regulatory Associate, at 614-272-4709.

Respectfully,

Elizabeth A. Ernst
Associate Director, DRA-Multisource Products

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Fax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

N/MC

July 13, 2004

Attention: Thuyanh (Ann) Vu

Controlled Correspondence
ANDA 76-387
Clotrimazole Troche, 10 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Fax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Vu:

In regard to our telephone conversation today with you, Mr. Jim Fan, and Mr. Paul Schwartz, we are submitting a commitment to complete a CBE supplement for ANDA 76-387 for Clotrimazole Troche, 10 mg. In accordance with your request we will submit the supplement within 30 days after we receive notification of product approval. The supplement will contain the following information:

- Particle size method for drug substance
- Validation report for particle size method
- Revised drug substance specification with particle size limits

Additionally, we commit to particle size testing for all drug substance lots received in-house when the method is validated.

We have also submitted a copy of this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Rebecca Braatz, Regulatory Associate, at 614-272-4709.

Respectfully,

Elizabeth A. Ernst
~~Associate~~ Director, DRA-Multisource Products

Boehringer Ingelheim
Roxane Laboratories

7.1

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Radhicka Rajagopalan

ORIG AMENDMENT
N/AA

July 26, 2004

Telephone Amendment
ANDA 76-387
Clotrimazole Troche, 10 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone 614-272-4785
Fax 614-276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Dr. Rajagopalan:

In response to your telephone contact on July 23, 2004, we are amending ANDA 76-387, Clotrimazole Troche, 10 mg. Attached please find the following:

- Roxane Laboratories' Drug Product Specification No. 1278-08, Clotrimazole Troche, 10 mg (revised to remove —)
- Roxane Laboratories' Stability Commitment and Protocol for Clotrimazole Troche, 10 mg (revised to remove —)

We will follow up this fax response with a hard copy sent to your attention, which will include the samples you requested, a 70-count bottle and a blister package of Clotrimazole Troche, 10 mg.

We have also submitted a letter of notice for this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Rebecca Braatz, Regulatory Associate, at 614-272-4709.

Respectfully,

Elizabeth A. Ernst
~~Associate Director~~,
DRA-Multisource Products

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