CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-387

BIOEQUIVALENCE REVIEW(S)

Review of a Bioequivalence Study with Clinical Endpoints

ANDA 76-387
Drug Product: Clotrimazole Troche, 10 mg
Sponsor: Roxane Laboratories, Inc.
Reference Listed Drug: Mycelex® Troche/Lozenge (Bayer), NDA 18713
Reviewer: Carol. Y. Kim, Pharm.D.
Submission dates: 3/28/02; 7/17/03 & 9/16/03 (electronic datasets)
Date of Review: December 12, 2003
V:/firmsnz/roxane/ltrs&rev/76387A.mor0302

I. Introduction

Clotrimazole is a synthetic broad-spectrum antifungal agent effective against oral lesions caused by *Candida* species. The troche dosage form is indicated for the local treatment of oropharyngeal candidiasis. After oral administration of a 10 mg clotrimazole troche to healthy volunteers, clotrimazole concentrations persist in saliva for up to three hours following the approximately 30 minutes needed for a troche to dissolve. Due to reported elevation of SGOT levels (15% of patients studied), periodic assessment of hepatic function is advised. Clotrimazole is also available as topical cream, lotion, solution and vaginal tablets.

Oral *Candidiasis*

Clinical signs of oral *Candidiasis* (also known as oral thrush) include diffuse erythema and white curd-like patches or plaques that appear as discrete lesions on the surfaces of the buccal mucosa, throat, tongue, and gums. Oral thrush caused by *Candida* species is usually painless, but fissuring at the corners of the mouth can be painful. Oral thrush is common in acute HIV infection and becomes increasingly common as the CD4+ cell count falls. At CD4+ counts <50/ L, esophageal thrush also becomes common. Oropharyngeal thrush is particularly likely to occur in neonates and in patients with diabetes mellitus, HIV infection, or dentures. Demonstration of pseudohyphae on wet smear from scraping of oral mucosa and positive fungal culture confirms the diagnosis of oral *candidiasis*.

II. Background

The sponsor submitted the original protocol CLO-0199 on January 6, 2000. Following the review of the protocol, the Office of Generic Drugs (OGD) commented on March 21, 2000 that the placebo arm should be included in the study and the primary endpoint should be a total cure (both mycological and clinical cure) at Day 15 (one day post-treatment). After further discussions with the Division of Dermatologic & Dental Drug Products (DDDDP/HFD-540) and the Division of Special Pathogen and Immunologic Drug Products (DSPIDP/HFD-590), the OGD recommended (P 00-001 & P 00-001B, 6/22/00 & 7/31/00) that a placebo group is not appropriate for this study, and the primary endpoint should be the clinical outcome at approximately 7 days post therapy.

The affected HIV population tends to have relatively advanced disease such that deferring therapy by giving placebo was not considered to be safe or ethical. The OGD also clarified (P 00-001C, 9/18/00) that the study treatment should be given for a total of 14 days and the primary endpoint should be the outcome of the clinical response at Day 21 in the evaluable population.

This is a first generic application for this product. The following IND and protocols have been previously reviewed by the OGD:

99-005 (Roxane): 2/12/99
IND [redacted] (Paddock Lab): 3/14/00

III. Study Information

Protocol Number: CLO-0199

The review of this protocol is included below with revisions to the original protocol in italics.

Title: A Prospectively Randomized, Blinded, Parallel Group Study of Clotrimazole Troches vs. Mycelex® Troches (10 mg troches five times a day for 14 days) in Patients with Human Immunodeficiency Virus (HIV) Infection for the Treatment of Oropharyngeal *Candidiasis*.

Objective: To compare the efficacy and safety of Roxane's clotrimazole troches to Mycelex® troches in HIV positive patients with oropharyngeal candidiasis that has been diagnosed by clinical examination and confirmed by fungal culture following 14 days of treatment.

Study Design:

This is a multi-center, randomized, *investigator-blind*, parallel-group design comparing the following two products:

1. Test: Clotrimazole Troches, 10 mg- Roxane Laboratories, Inc.
2. Reference: Mycelex® (clotrimazole) Troches, 10 mg – Bayer

- *The following lot numbers were used in the study:*

1. *Test: Clotrimazole Troches, 10 mg- Roxane Laboratories, Inc., lot # 019011*
2. *Reference: Mycelex® (clotrimazole) Troches, 10 mg – Bayer, lot # 019002A*

Except for one patient (108-9999; Ref), all patients were randomized to receive either Roxane's Clotrimazole Troche or Mycelex® Troche. A single troche was administered as a lozenge to be dissolved in the mouth five times daily for fourteen days. The timing for dose administration was not specified in the protocol.

Identity of Products

Roxane received 125 bottles of 140 Mycelex® 10 mg troches per bottle (Bayer lot #9dFP) from their vendor. Of these, 11,320 troches were repackaged into foil pouches (strips of 10 each) identified with Roxane lot #019002A. Each pouch was labeled and four strips (40 troches) were placed in each of 283 plain white cartons. These 283 cartons were shipped to ——— ——— February 2, 2001.

Roxane manufactured and packaged 11,320 troches into foil pouches. Each pouch was labeled and four strips (40 troches) were placed in each of 283 plain white cartons. These 283 cartons were shipped to ———, on March 13, 2001.

——— Quality Assurance personnel then pulled six kits per random list provided by the ——— biostatistician and labeled them as retention samples. The ——— biostatistician received one kit from each arm to confirm the appropriate treatment arms. Except for ——— biostatistician and Quality Assurance personnel at ———., all investigators and study staffs were blinded.

Reviewer's Comments: *Double-blinding was not feasible because the innovator's product has the brand name stamped into each individual troche. Therefore, blinding of the investigator and study staff was achieved by packaging each troche in a foil pouch.*

Study Population:

Male and Female Patients with HIV positive status. Patients must meet the following criteria to be enrolled in the study:

Inclusion Criteria

- Documented HIV positive status;
- Clinical examination of oropharynx is consistent with diagnosis of oral Candidiasis (such as creamy, white, curd-like patches or erythematous lesions on mucosal surfaces);
- Findings on direct microscopic examination (potassium hydroxide smear) consistent with Candida species OR positive fungal culture for Candida species, with culture obtained in the 2 days preceding initiation of therapy with the study drug;
- Male or female patient >/= 18 years;
- For women of childbearing potential: negative blood or urine pregnancy test AND agreement to use adequate contraception (investigator's discretion) while on study drug;
- Mental status allows comprehension of instructions for troche administration;
- Written informed consent.

Exclusion Criteria

- Signs or symptoms suggestive of esophageal *Candidiasis* (such as dysphagia or odynophagia) UNLESS the results of an endoscopic evaluation of the esophagus are negative;
- Presence of perioral lesions only;
- Use of other antifungal agents within 5 days of enrollment to the study;
- Pregnant or lactating women;
- History of hypersensitivity to imidazole or azole compounds;
- Patient unwilling or unable to be followed at the study center for the duration of the study (*3 weeks*);
- Patient had received an investigational drug in the last 30 days;
- Treatment with another investigational drug was planned within the next *three weeks.*

Early Termination

The following criteria led to treatment termination:

- Side effects related to troche administration prevent continuation;
- In patients with any elevated liver function test at baseline (defined as SGOT/AST, alkaline phosphatase or bilirubin >/= 3X upper limit of normal for the institution), if the liver function test on Day 8 was >/= 2X its value at baseline, treatment was to be discontinued, unless the result could be explained by another medical condition. If this situation occurred, the patient was to be immediately notified to stop taking the study medication, and to come in for an off-study evaluation (to collect study medication, assess and record Adverse Events, and repeat hematology and chemistries);
- Positive fungal culture of the oropharynx at the End of Treatment (Day 15) evaluation (which would presumably require systemic antifungal therapy);
- Requirement for systemic antifungal therapy for another medical diagnosis or condition (systemic antibacterial or antiviral therapy is allowed);
- Investigator decision that withdrawal from the study was in the patient's best interest;
- Patient's decision to withdraw from the study;
- Non-compliance with study medication (defined as: evidence that the patient had taken <50% of the assigned dose of study medication);
- Patient was lost to follow-up.

Early Termination Evaluations

If the patient terminated before Day 8, hematology, chemistries, and a targeted physical examination, were to be completed in addition to the Day 8 evaluation. If the patient terminated *between Day 9 and Day 15,* a targeted physical examination, and measurement of Albumin/Creatinine were to be completed in addition to the Day 15 evaluation. If the patient terminated between Day 16 and Day 21, all Day 21 evaluation was to be performed.

Study Procedures:

Study Visits

Screening (Day 0): Patient eligibility was determined. A medical history with symptoms of oral *Candidiasis*, examination of oropharynx, pregnancy tests if indicated, and KOH examination of buccal smear were to be completed prior to randomization. Patient consent form was completed. The above procedures were completed within 1 day prior to registration.

Baseline (Day 0): After completion of screening procedure, the investigator was instructed to follow the registration procedure for a patient. The request for registration was faxed to Boehringer Ingelheim (BI) and BI then faxed the request to ——————. A confirmation of registration with the assigned randomization number was returned to the site and also faxed back to BI.

Each patient was instructed to complete vital signs, a targeted physical examination, hematologies, chemistries, and a fungal culture of the oropharynx within 2 days of enrollment.

Day 8 (+/- 1 day) Evaluation: Symptoms of oral *Candidiasis*, examination of the oropharynx, vital signs, liver function tests, adverse events, drug accountability, and compliance were assessed. If the patient had not had a clinical response defined as improvement in both symptoms of oral *Candidiasis* and examination of the oropharynx, the patient was terminated from the study.

Day 15(+/- 1 day)Evaluation; *End of Treatment*: This visit was scheduled on the day after the completion of study medications. Patients were evaluated for symptoms of oral Candidiasis and the examination of oropharynx. Vital signs, hematologies, chemistries and fungal culture of oropharynx were collected. Adverse events, drug accountability, and compliance were also evaluated.

***Day 21(+/- 1 day)Evaluation; 7 day follow-up visit (primary endpoint)*:** This evaluation was only for patients who completed the assigned treatment and had a negative fungal culture at the Day 15 visit. The following procedures were completed at this visit: evaluation of symptoms of oral *Candidiasis*, examination of the oropharynx, vital signs, targeted physical exam, hematologies, chemistries, adverse events, and fungal culture of the oropharynx.

For statistical purpose, the presence or absence of seven clinical signs and symptoms were recorded on the case report form at baseline (Day 0), Day 8, Day 15, and Day 21 as follows:

A. Erythematous areas
B. White patches
C. Mouth pain
D. Altered taste
E. Pruritus
F. Dysphagia
G. Odynophagia

Evaluation of Clinical Response

- Clinical Response–"complete disappearance of all oral lesions and all symptoms originally attributed to the diagnosis of oral *candidiasis*". (vol. 1.1, p. 95)
- No Response- An outcome that was not identified as Clinical Response was considered a FAILURE for statistical purposes.

If the clinical outcome at Day 8 was not improved or worsened based on oropharynx examination and present symptoms of candidiasis, the patient was to be discontinued and considered as TREATMENT FAILURE (no response).

If the clinical response of Day 21 showed complete disappearance of all oral lesions and all symptoms originally attributed to the diagnosis of oral *candidiasis*, the patient was to be considered as Clinical Response, regardless of the result of fungal culture of oropharynx on Day 21.

Evaluation of Fungal Culture

- Fungal culture of oropharynx was scheduled at baseline, Day 15 and Day 21.

Patients with positive fungal culture of oropharynx at Day 15 were discontinued and not returned for Day 21 evaluation.

Reviewer's Comments:

The 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*
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 require further treatment in the absence of clinical evidence of disease 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.

Patients that were discontinued because of positive fungal cultures at Day 15 despite clinical outcome of cure or "improved" at that time should be considered as unevaluable and excluded from the PP population. Patients that were discontinued because of positive fungal cultures at Day 15 should be carried forward as treatment failures only if they had no clinical improvement

or worse clinical signs and symptoms at that time. If clinical evaluation data are available at the Day 21 visit for any of these patients, then they should be included in the PP analysis according to their clinical outcome at Day 21.

Concomitant medication

Concomitant medications were allowed at the investigator's discretion to treat the underlying patients' medical conditions other than fungal infections. If the patient required treatment for fungal infections other than oral *candidiasis*, they should be discontinued from the study.

Compliance

Each patient was given a one-week supply of the study medications at baseline and Day 8 visits. The Diary cards were given to patients to record the medication intakes. The dispensing information, diary cards, and returned troche counts served as basis for determining the compliance rate of dosing. Patients with compliance rate of 50% and greater of the prescribed dose for the 14-day study period were considered compliant.

Reviewer's Comments: *Although the visit window was specified in the final protocol as +/- 1 day for all post-baseline evaluation visits, the sponsor included patients who completed the post-baseline evaluation visits within -3 days to +8 days in the PP population. The clinical outcome from these visits, beyond the originally specified visit window, was consistent with the response given in the previous or the following evaluation visits. Therefore, including the clinical response from these extended visit windows is not likely to change the outcome of the study if they did not violate any other protocol criteria. The clinical study (Dr. ———) evaluated for the approval of Mycelex® Troche, 10 mg, included patients with the visit window up to +10 days in the PP population.*

Safety:

The primary safety measures were assessed during the study using the documentation of adverse events and the laboratory parameters (hematology, liver function test, and creatinine). All adverse events were reported on Case Report Form (CRF) and the severity of each event was classified using the National Cancer Institute Common Toxicity Criteria Scale (vol. 1.1, pp. 111-134). Any serious adverse events (SAE) were reported to ——— and Boehringer Ingelheim Drug Safety-South Africa. ——— was responsible for the review and notification of these events to the FDA and the sponsor. Boehringer Ingelheim Drug Safety-South Africa was responsible for the review, notification of these events to the South African Medicines Control Council, and maintenance in their drug safety database.

Statistical Plan:

Primary Endpoint

The primary endpoint is the rate of Clinical Cure ("Clinical Response") at Day 21 in the PP population.

Clinical Cure: Complete disappearance of all oral lesions and all symptoms originally attributed to the diagnosis of oral *candidiasis* at the Day 21 evaluation.

Failure: no response of oral lesions and symptoms at either Day 8 or Day 21, regardless of fungal culture results. According to the protocol, treatment Failure at Day 15 due to positive fungal culture (sponsor discontinued them prior to Day 21 evaluation) should be carried forward as Failure at Day 21.

Reviewer's Comments: *Clinical Cure is used interchangeably with the sponsor's term of clinical response in this review. For the statistical purpose, only two efficacy outcomes were considered, Clinical Cure or Failure.*

Secondary

- Negative fungal cultures of the oropharynx for *Candida* species 7 days after the end of treatment (follow-up) in the PP population.
- Negative fungal cultures of the oropharynx for *Candida* species after 14 days of treatment (end of treatment) in the ITT and PP populations.
- Clinical response (by symptom assessment and physical examination) after 7 and 14 days of treatment.
- Compliance with treatment as assessed by troche count and patient review.

Reviewer's Comments: *The primary comparative efficacy measure in this study is whether or not the patient is judged to be clinically cured (clinical response) at day 21 (7-days post treatment). Those patients that were discontinued due to positive fungal culture results at the end of treatment and identified as "treatment failure" at visits prior to Day 21 evaluation should be carried forward as "failure" in the PP population analysis only if they were also evaluated as clinical failures. Any patient that was discontinued because of positive fungal culture at Day 15 but had clinical response of cure or improved should be excluded from the PP population analysis if Day 21 data are missing. Any patient that was discontinued because of positive fungal culture and no clinical improvement or worse clinical signs and symptoms should be carried forward as failure in the PP population analysis.*

The secondary comparative efficacy measure, the outcome of fungal culture results at Days 15 and 21, and clinical response (complete disappearance of all signs and symptoms) at Day 15 for the PP population should be considered supportive information.

Sample Size

The sample size of 87 enrolled patients per treatment group (total 174) was originally proposed based on the assumed cure rate of 0.50 for both the test and reference treatments due to negative *Candida* culture results with Mycelex^{R} troches reported to be between 20-50%. *However, based on early assessment of patient dropout rate exceeding the estimated 15%, the sample size was increased to 189 prior to enrollment.*

Analysis

Nominal variables such as gender and race were compared with the Chi-square test or Fisher's exact test. For continuous variables, treatment group comparisons were carried out using analysis of variance methods. The factors for the analysis of variance are age, performance status, WBC, absolute neutrophil count and % lymphocytes.

The following evaluable patients were assessed for Cure or Failure at Day 21: 1) met the Inclusion/Exclusion Criteria, 2) compliant with the study treatment ($\geq$50%), and 3) no protocol violations that would prejudice the outcome assessment. Treatment failure at Day 8 or Day 15 was carried forward in the final analysis.

The clinical equivalence of the test and reference was based on the Cure rate (clinical response) at Day 21 and was established using dichotomous outcome of response and non-response in the two treatment arms. The data were analyzed using the Chi-square test and expressed as the one-sided 90% CI (α=0.05) of the difference in response.

Reviewer's Comments: *The FDA statistician was consulted for applying appropriate statistical method for this study. Using Yate's 90% continuity correction, the proportional difference between the test and the reference clinical cure rates at the primary endpoint (7-days follow-up; Day 21) should be contained within (-.20 and +.20) to be deemed bioequivalent.*

IV. RESULTS

CRO: Both [redacted] and Boehringer Ingelheim monitored the study. [redacted] was responsible for the overall study management, including the process for supplying and repackaging of the reference products. Boehringer Ingelheim-South Africa was responsible for the study site management.

Study Centers (multiple places in South Africa) and Investigators:

Site No.	N	Investigator	Site
0101	32	Dr.	
0102	16	Dr.	
0103	17	Dr.	
0104	21	Dr.	
0105	4	Dr.	
0106	X	Dr.	
0107	40	Dr.	
0108	11	Dr.	
0109	X	Dr.	
0110	16	Dr.	
0111	10	Dr.	
0112	12	Dr.	
0113	10	Dr.	

X= The sponsor reported that no patient was enrolled from this site.

Study Period: May 4, 2001-November 27, 2001

Reviewer's comment: *In response to the sponsor's telephone request on June 26, 2000, the Agency accepted the sponsor's proposal to conduct the study outside of the United States (see P#00-001 for details).*

Subject Enrollment:

A total of one hundred eighty-nine patients (189) were enrolled in the study; 95 were in the test group (Roxane) and 94 in the reference group (Mycelex® Troche). Of these, one patient (#9999, site 108; ref) was not randomized but received the study drug. One patient from each treatment group did not receive the study drug. Based on the sponsor's report, a total of 101 patients (50 in the test and 51 in the reference group) were treated and completed the study for 21 days. The sponsor's analysis of the distribution of patients per treatment arm is shown in Table I. This reviewer's analysis of the distribution of patients per treatment arm for each analysis population is shown in Table II.

APPEARS THIS WAY
ON ORIGINAL

TABLE I – DISTRIBUTION OF PATIENTS TO TREATMENT ARMS BY ANALYSIS POPULATION (PER SPONSOR)^

Reason for Discontinuation	Roxane's Clotrimazole Troche (N)	Mycelex[R] Troche (N)	Total (N)
Enrolled	95	94	189
Positive Day 14 culture	-27*	-26	53
Lost to Follow-up (LTFU)	-8	-5	13
Death	-3	-1	4
Adverse events	-1	-3	4
No clinical improvement	-1	0	1
Non-compliance	-1	0	1
Patient withdrew or unable to return	-3	-7	10
Removed in error	-1	-1	2
Total no. of patients discontinued	45	43	88
Total no. of patients completed	50	51	101

^per data listed under Appendix 16.2.1: Disposition Summary (Patients who left study prior to Day 21) vol. 1.2, pp. 520-522

*The patient #1006 (site 102) was also hospitalized with TB.

TABLE II – DISTRIBUTION OF PATIENTS TO TREATMENT ARMS BY ANALYSIS POPULATION (PER REVIEWER)#

Population	**Roxane's Clotrimazole Troche** N	**Mycelex® Troche** N	**Total** N
Enrolled	95	94	189
Not treated*	-1	-1	2
Lost to follow-up after medication dispensed**	-1	-1	2
Safety	93	92	185
Not randomized#*	0	-1	1
Death and no post-baseline visit data***	-1	0	1
Baseline fungal culture negative	-5	-5	10
Baseline fungal culture not done	-4	-5	9
Intent-to-Treat (ITT) ^	83	81	164
Death^** (post-baseline visits available)	-2	-1	3
Non-compliance##	-1	0	1
Lost to follow-up/prematurely discontinued at least one post-baseline visit available)	-7	-4	11
emoved from the study in error	-1	-1	2
Patient could not return for personal reasons	-2	-3@	5
Scheduling error (day 21 visit not scheduled)	0	-1	1
Protocol violation$	0	-2	2
Discontinued due to adverse events	-1	-2	3
^^Per Protocol (PP)	69	67	136

#Based on data presented in Appendix 16.1.7 (treatment); 16.1.2 (disposition summary of discontinued patients); 16.2.2 (protocol deviation); 16.2.3 (study exclusions); 16.2.6d (fungal culture).

*One patient from each treatment group did not receive the study medication. Patient #1005 (site 104, T) withdrew consent and patient #1001 (site 110, Ref) didn't come to collect the study drug.

**Patients #1009 (site 101, T) and #1015 (site 101, Ref) received the study drugs but never returned for post-baseline evaluation.

#*Patient #9999 (site 108, Ref) was treated and later discontinued due to adverse events (serious pneumonia and vomiting) reported to be "definitely not related" to the study drug.

***Patient #1004 (site 113, T) died due to reason unrelated to the study drug prior to Day 8 visit. This patient took 4 doses of Roxane Troche.

^Included all patients who received at least 1 troche of the study medication and completed at least one post treatment visit.

^**Patients #1016 (site 104, T), 1007 (site 107, Ref), 1006 (site 112, T) died due to reason unrelated to the study drugs. The clinical responses on visits prior to death were considered "cure" for these patients.
Patient #1006 (site 110) was discontinued due to completion of Day 8 visit outside of the scheduled visit window (+3 day).
@Patient #1001 (site 111, Ref) was not compliant (took the medication only up to Day 8 visit) and discontinued the study drug. Two weeks after completion of the last dose of the study drug, the patient died of intracranial infection unrelated to the study medication. The fungal culture was negative and clinical signs and symptoms were absent at Day 15 visit prior to death.
$Patient #1035 (site 107, Ref) received prohibited medication (Amphotericin IV) during the study. Patient #1038 (site 107, Ref) received prohibited medication (Clotrimazole Cream) during the study.
^^Met inclusion/exclusion criteria, had baseline fungal culture positive for Candida, took at least 50% of prescribed study drug, didn't drop out of the study prior to Day 21 for reasons other than treatment failure or adverse event, and had no significant protocol violation.

The equivalence analysis was conducted on the PP population. Safety analyses were conducted on the ITT population.

Reviewer's comments:

Deaths

- *A total of six patients died in the study unrelated to the study drug. The sponsor included the following four patients in the PP population analysis as "treatment failure": #104-1016 (T), 107-1007 (Ref), 112-1006 (T), 113-1004 (T). Since they were discontinued from the study due to reason unrelated to the study drug, they should be excluded from the PP analysis and not included as "treatment failure".*
- *Two weeks after the completion of the last dose at Day 8, patient #111-1001 (Ref) died of intracranial infection. Since this patient's Day 15 clinical and fungal culture evaluations were available, the sponsor included this patient in the ITT population only. Day 21 data are not available. This reviewer agrees with the sponsor's decision not to include this patient in the PP analysis.*
- *Patient #108-9999 (Ref) was not randomized but received the reference drug and completed the Day 8 visit prior to death unrelated to the study drug. After completion of 13 days of the study drug, the patient died of bronchopneumonia. This patient should be included in the safety population but excluded from the ITT and PP population analyses.*

Per protocol exclusions

- *The sponsor discontinued patients who had positive fungal culture at Day 15 regardless of absence of all clinical signs and symptoms on Day 15 clinical evaluation and included them in the PP population analysis as "treatment failure". Since the primary endpoint of this study is the clinical response of cure the appropriate management of these patients was to continue them in the study to complete the Day 21 visit if the clinical signs and symptoms at Day 15 were " improved" or " absent".*

Standard of care for immunocompromised patients with oral candidiasis does not require further systemic treatment of patients with positive fungal culture at the end of treatment if their clinical signs and symptoms have resolved. The positive fungal culture, particularly in the immunocompromised population, may represent colonization with Candida species and not clinical infection. Therefore, these patients should not be considered treatment failures unless they also had no improvement or worse clinical signs and symptoms.

A total of 52 patients were discontinued because of positive Day 15 cultures, and they were equally distributed between the treatment groups [26/95 (27%) of test and 26/94 (28%) of reference patients]. Of these, 35 patients [18/26 (69%) of test and 17/26 (65%) of reference] were considered clinical cures at Day 15, 8 (4 per group) were "improved", and 9 (4 Test, 5 Ref) either developed new signs and symptoms or worsened at Day 15. Data at Day 21 are available for six of the patients with a clinical cure but positive culture at Day 15. All 6 continued to have positive fungal cultures, and half (2 Test, 1 Ref) developed new clinical signs and symptoms. The other half (all 3 Ref) were considered clinical cure at day 21.

Given that a positive fungal culture at Day 15 does not reliably predict a clinical failure at Day 21, it is not appropriate for these patients to be analyzed as failures. Given that the patients in question are equally distributed between test and reference groups, along with the fungal cure meeting bioequivalence limits at Day 15 (according to the sponsor's analysis), it is unlikely that exclusion of these unevaluable patients from the per protocol population would introduce a significant bias into the analysis of this study. 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 (or 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. Those with data available at Day 21 should be analyzed according to the Day 21 evaluation for primary endpoints and according to the Day 15 evaluation for secondary endpoints.

On June 19, 2003, the OGD consulted the Division of Special Pathogen and Immunologic Drug Products (DSPIDP: HFD-590) to confirm the appropriate evaluation of treatment efficacy in oropharyngeal candidiasis. In a memorandum dated June 20, 2003, the medical officer from the DSPIDP confirmed that mycological eradication of Candida in orophayngeal candidiasis is difficult to accomplish especially in patients that are highly immunosupressed. In addition, it is recognized that in these patients, clinical improvement occurs despite microbiological persistence. Therefore, based on the natural history of oropharyngeal candidiasis and current standards of medical practice for oropharyngeal candidiasis, DSPIDP concurs with the OGD's position for excluding those discontinued patients regardless of clinical outcome at Day 15 from the evaluable population analysis. DSPIDP also concurs that it is appropriate to retain patients as failures if they were discontinued as early "clinical" treatment failures for the primary efficacy analysis.

- *Although patient # 1007(site 102, T) had a clinical response considered to be cure on the Day 21 visit, the fungal culture was not performed on Day 15. Therefore, the sponsor excluded this patient from the PP population analysis based on the protocol. Since the fungal culture at Day 15 may have no impact on the primary endpoint, this patient should be included as a cure instead of excluded for the primary endpoint. However, this patient should be considered unevaluable for the secondary endpoint of fungal culture at Day 15.*

- *Per protocol, any patients who discontinued due to not improved or worsened clinical outcome at Day 8 based on oropharynx examination and persistent symptoms of candidiasis should be treated as "failure" in the PP population analysis (Day 21).*

- *The sponsor identified the following three patients that were discontinued due to adverse events as treatment failures: #1030 (site 101, Ref), #1002 (site 112, Ref), and #1008 (site 113, T). These patients discontinued the study drug because of unpleasant adverse events and not due to lack of treatment effect. Therefore, these patients should be excluded from the PP population analysis.*

- *The sponsor defined ITT population including all patients who were registered and randomized to treatment, regardless of whether study drug was ultimately given, and one patient who was not randomized but received the study drug (#-9999, site 108). To maintain the consistency of the review with previous bioequivalence studies with clinical endpoints, this reviewer defined ITT population including all patients who received at least 1 troche of the study drug and completed at least one post-treatment visit. Therefore, the sponsor's designated ITT population is relabeled as all enrolled patients in this review.*

- *Patient #1038 (site 107, Ref) received prohibited medication (topical clotrimazole cream) during the study, but the sponsor included this patient in the evaluable population. Due to violation of protocol, this patient should be excluded.*

Demographics:

Out of 189 patients enrolled in the study, 73 were male and 116 were females. Baseline demographics, age, gender, and race were comparable in the two treatment groups. The mean age was 33.5 (19-53) and 35 (18-73) years for the test and reference products, respectively. The demographic characteristics for all enrolled patients, including patient #9999 (site 108) not randomized to the study, were similar to the PP population. See Table III for the demographic characteristics for all enrolled patients.

Table III: Demographic Characteristics of All Enrolled Patients (per sponsor)[1]

	Treatment	N	Mean ± s.e.	Range		
Age	Roxane	95	33.5 ± 7.4	19-53		p = 0.15
	Mycelex®	94	35.2 ± 9.0	18-73		(One-way ANOVA)
	Total	189	34.3 ± 8.2	18-73		
	Treatment		**Black N (%)**	**Mixed Race[2] N (%)**	**Caucasian N (%)**	
Race	Roxane	95	78 (82.1%)	6 (6.3%)	11 (11.6%)	
	Mycelex®	94	80 (85.1%)	1 (1.1%)	13 (13.8%)	p = 0.01
	Total	189	158 (83.6%)	7 (3.7%)	24 (12.7%)	(Fisher's Exact Test)
	Treatment		**Male N (%)**	**Female N (%)**		
Sex	Roxane	95	42 (44.2%)	53 (55.8%)		$X^2 = 2.51$
	Mycelex®	94	31 (33.0%)	63 (67.0%)		df = 1
	Total	189	73 (38.6%)	116 (61.4%)		p = 0.11

[1]All patients who were registered and randomized to treatment, regardless of whether study drug was ultimately administered, and one patient (site 108, patient 9999) who was not randomized but who received study drug.
[2]Based on South African use of the term "colored" to mean "mixed race", this category included patients who were described as "colored" under the choice "other race" on the demographics case report form.

Baseline Disease Severity:

The Sponsor tabulated the baseline hematology values and clinical signs and symptoms for all enrolled patients in Table IV a. and Table IV b. The mean for the baseline hematology values were not statistically different in the two treatment groups. The number of patients under each category of clinical signs and symptoms was comparable between the two treatment groups.

Table IV a: Baseline Hematology Values In All Enrolled Patients (per sponsor)[1]

	Treatment	N	Mean	Range	p-value
Total White Blood Cells (10^9/L)	Roxane	94	5.08	1.30-15.10	0.37
	Mycelex®	93	4.74	0.20-16.70	
Neutrophils (10^9/L)	Roxane	94	3.17	0.50-11.90	0.32
	Mycelex®	93	2.84	0.20-13.28	
Lymphocytes (10^9/L)	Roxane	94	1.23	0.20-4.50	0.93
	Mycelex®	93	1.24	0.20-3.80	
Platelets (10^9/L)	Roxane	92	272	60-804	0.87
	Mycelex®	94	275	70-627	
Hemoglobin (g/dL)	Roxane	94	11.4	7.6-16.6	0.94
	Mycelex®	94	11.4	5.9-16.4	
CD4 (10^9/L)	Roxane	92	0.11065	0.00030-0.79000	0.39
	Mycelex®	89	0.12885	0.00052-0.63200	

[1]All patients who were registered and randomized to treatment, regardless of whether study drug was ultimately administered, and one patient (site 108, patient 9999) who was not randomized but who received study drug.

Table IV b: Presence of Baseline Signs and Symptoms Among All Enrolled Patients (per sponsor)[1]

	Roxane (N = 95) n (%)	Mycelex® (N = 94) n (%)	Total (N = 189) n (%)	
Erythematous Areas	55 (57.9%)	56 (59.6%)	111 (58.7%)	$X^2 = 0.06$ df = 1 p = 0.81
White Patches	94 (99.0%)	92 (97.9%)	186 (98.4%)	$X^2 = 0.35$ df = 1 p = 0.55
Mouth Pain	56 (59.0%)	52 (55.3%)	108 (57.1%)	$X^2 = 0.25$ df = 1 p = 0.61
Altered Taste	65 (68.4%)	62 (66.0%)	127 (67.2%)	$X^2 = 0.13$ df = 1 p = 0.72
Pruritus	33 (34.7%)	25 (26.6%)	58 (30.7%)	$X^2 = 1.47$ df = 1 p = 0.22
Dysphagia	0	0	0	
Odynophagia	0	0	0	
Other Signs	5 (5.3%)	4 (4.3%)	9 (4.8%)	p = 0.25 (Fisher's Exact Test)
Other Symptoms	7 (7.4%)	2 (2.1%)	9 (4.8%)	p = 0.07 (Fisher's Exact Test)

[1] All patients who were registered and randomized to treatment, regardless of whether study drug was ultimately administered, and one patient (site 108, patient 9999) who was not randomized but who received study drug.

Efficacy Outcomes:

The Sponsor's primary analysis of clinical outcome at Day 21 for the PP population is shown in Table V. The sponsor's table included the 90% CI for the proportional cure rate comparing the test and the reference products. The sponsor claimed to use Wald's method with Yate's continuity correction for the calculation of the 90% CI. The secondary analyses of clinical outcome and fungal culture results at Day 15 and Day 21 for the PP population are shown in Table VI a-c.

Table V: Primary Efficacy Endpoint: Day 21 Clinical Response, Evaluable Patients (per sponsor)[1]

Treatment	Response; n (%)	No Response; n (%)
Roxane (N = 72)	34 (47.2%)	38 (52.8%)
Mycelex® (N = 71)	32 (45.1%)	39 (54.9%)
Total (N = 143)	66 (46.2%)	77 (53.8%)

[1] Patients were defined as evaluable if all of the following criteria were met: they had a baseline fungal culture positive for Candida, they did not drop out of the study prior to day 21 for reasons other than treatment failure or adverse events, they took at least 50% of prescribed study drug (with the exception of patients who dropped out due to adverse events), and they did not have any major protocol violations.

Chi-squared Test:
$X^2 = 0.07$
df = 1, p = 0.80

Difference in Percent Response:
Point Estimate = 2.2%
90% C.I. = (-11.6%, 15.9%)

Table VI a: Secondary Efficacy: Day 15 Clinical Response, Evaluable Patients (per sponsor)[1]

Treatment	Response N (%)	No Response n (%)
Roxane (N = 72)	51 (70.8%)	21 (29.2%)
Mycelex® (N = 71)	57 (80.3%)	14 (19.7%)
Total (N = 143)	108 (75.5%)	35 (24.5%)

[1] Patients were defined as evaluable if all of the following criteria were met: they had a baseline fungal culture positive for Candida, they did not drop out of the study prior to day 21 for reasons other than treatment failure or adverse events, they took at least 50% of prescribed study drug (with the exception of patients who dropped out due to adverse events), and they did not have any major protocol violations.

Chi-squared Test:
$X^2 = 1.73$
df = 1
p = 0.19

Difference in Percent Response:
Point Estimate = -9.4%
90% C.I. = (-21.2%, 2.3%)

Table VI b: Secondary Efficacy: Day 21 Fungal Culture Results, Evaluable Patients (per sponsor)[1]

Treatment	Response[2] n (%)	No Response[3] n (%)
Roxane (N = 72)	30 (41.7%)	42 (58.3%)
Mycelex® (N = 71)	20 (28.2%)	51 (71.8%)
Total (N = 143)	50 (35.0%)	93 (65.0%)

[1] Patients were defined as evaluable if all of the following criteria were met: they had a baseline fungal culture positive for Candida, they did not drop out of the study prior to day 21 for reasons other than treatment failure or adverse events, they took at least 50% of prescribed study drug (with the exception of patients who dropped out due to adverse events), and they did not have any major protocol violations.
[2] ***Negative Fungal Culture at day 21.***
[3] Positive Fungal Culture at day 21.

Chi-squared Test:
$X^2 = 2.86$
df = 1
p = 0.09

Difference in Percent Response:
Point Estimate = 13.5%
90% C.I. = (0.5%, 26.5%)

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Table VI c: Secondary Efficacy: Day 15 Fungal Culture Results, Evaluable Patients (per sponsor)[1]

Treatment	Response[2] n (%)	No Response[3] n (%)
Roxane (N = 72)	41 (56.9%)	31 (43.1%)
Mycelex® (N = 71)	37 (52.1%)	34 (47.9%)
Total (N = 143)	78 (54.6%)	65 (45.4%)

[1] Patients were defined as evaluable if all of the following criteria were met: they had a baseline fungal culture positive for Candida, they did not drop out of the study prior to day 21 for reasons other than treatment failure or adverse events, they took at least 50% of prescribed study drug (with the exception of patients who dropped out due to adverse events), and they did not have any major protocol violations.

[2]***Negative Fungal Culture at day 15.***

[3]Positive Fungal Culture at day 15.

Chi-squared Test:
$X^2 = 0.34$
df = 1
p = 0.56

Difference in Percent Response:
Point Estimate = 4.8%
90% C.I. = (-8.9%, 18.5%)

Reviewer's comments:

- *Patients should be defined as evaluable for the Day 15 results if they did not drop out of the study prior to Day 15. Absence of Day 21 data should have no impact on the endpoints at Day 15.*
- *The sponsor's analysis demonstrates that the 90% CI of the proportional difference in the primary endpoint, clinical cure rates at 7-day follow-up visit (day 21), is within (-.20, +.20). No placebo or vehicle group was included in the study design for the safety and efficacy reasons. Because the sponsor inappropriately included or excluded a large portion of patients from the ITT/PP population analysis, the 90% CI for the clinical cure rates should be recalculated, incorporating this reviewer's comments above. A statistical review was requested to verify the sponsor's data and for the reevaluation of the clinical outcome.*

Adverse Events:

A total of 182 adverse events were reported in the study; 48 (96 events) patients in the test and 49 (86 events) patients in the reference products. Three patients [#1030 (site 101, Ref), #1002 (site 112, Ref), 1008 (site 113, T)] had to discontinue the study drugs due to unpleasant adverse events (nausea/vomiting; allergic reaction; severe nausea/vomiting). The majority of the adverse events were reported as grade 1 or 2 severity. One event from each treatment group was grade 3 drug-related event (hepatitis with test and elevation of SGPT with the reference). Although statistical comparison between the treatment groups was not performed for adverse events, a lower number of patients had nausea (2/93 T; 10/92 Ref) and vomiting (4/93 T; 7/92 Ref) and a higher number had anemia (5/93 T; 1/92 Ref) with use of the test product. The sponsor's analysis of adverse events by body system and severity are shown below in Table VII.

Deaths

Six deaths, three from each treatment group, were reported in the study caused either by the progression of the underlying HIV disease, related opportunistic infections or other complications. Additional 5 adverse events in 5 patients were reported to be serious, all in patients that received the test product. However, none of the deaths or serious adverse events was considered to be related to the study drug. The sponsor's summary of reported death and serious adverse events in the study is provided in Table VIII.

Table VII: Adverse Events by Treatment, Among Patients Evaluable for Safety (per sponsor)[1]

Body System	Preferred Term	Roxane (N = 93)			Mycelex® (N = 92)		
		X[2]	n[3]	(%[4])	X[2]	n[3]	(%[4])
Any Event		96	48	(51.61%)	86	49	(53.26%)
Body as a Whole	ABDOMINAL PAIN	2	2	(2.15%)	3	3	(3.26%)
	AIDS	0	0	(0%)	1	1	(1.09%)
	ASTHENIA	2	2	(2.15%)	1	1	(1.09%)
	BACK PAIN	1	1	(1.08%)	1	1	(1.09%)
	CACHEXIA	0	0	(0%)	1	1	(1.09%)
	CRYPTOCOCCOSIS	0	0	(0%)	1	1	(1.09%)
	FACE EDEMA	0	0	(0%)	1	1	(1.09%)
	FEVER	5	5	(5.38%)	2	2	(2.17%)
	FLANK PAIN	1	1	(1.08%)	0	0	(0%)
	FLU SYNDROME	3	3	(3.23%)	2	2	(2.17%)
	HEADACHE	2	2	(2.15%)	3	3	(3.26%)
	INFECTION	5	5	(5.38%)	6	6	(6.52%)
	INFECTION BACTERIAL	1	1	(1.08%)	0	0	(0%)
	PAIN	2	2	(2.15%)	1	1	(1.09%)
Cardiovascular System	HEART FAILURE	1	1	(1.08%)	0	0	(0%)
	HYPERTENSION	1	1	(1.08%)	0	0	(0%)
	PERICARDITIS	1	1	(1.08%)	0	0	(0%)
Digestive System	ANOREXIA	2	2	(2.15%)	1	1	(1.09%)
	APHTHOUS STOMATITIS	0	0	(0%)	1	1	(1.09%)
	BILIARY PAIN	0	0	(0%)	1	1	(1.09%)
	CHOLANGITIS	1	1	(1.08%)	0	0	(0%)
	CONSTIPATION	1	1	(1.08%)	1	1	(1.09%)
Digestive System (cont'd)	DIARRHEA	7	6	(6.45%)	4	4	(4.35%)
	DRY MOUTH	1	1	(1.08%)	2	2	(2.17%)
	DUODENITIS	1	1	(1.08%)	0	0	(0%)
	DYSPEPSIA	1	1	(1.08%)	2	2	(2.17%)
	ESOPHAGITIS	1	1	(1.08%)	0	0	(0%)
	GASTROENTERITIS	1	1	(1.08%)	1	1	(1.09%)
	GASTROINTESTINAL DISORDER	1	1	(1.08%)	0	0	(0%)
	GINGIVITIS	0	0	(0%)	1	1	(1.09%)
	HEPATITIS	1	1	(1.08%)	2	2	(2.17%)
	INCREASED APPETITE	1	1	(1.08%)	0	0	(0%)

Body System	Preferred Term	Roxane (N = 93)			Mycelex® (N = 92)		
		X[2]	n[3]	(%[4])	X[2]	n[3]	(%[4])
	JAUNDICE	1	1	(1.08%)	0	0	(0%)
	NAUSEA	2	2	(2.15%)	10	10	(10.87%)
	PAROTID GLAND ENLARGEMENT	1	1	(1.08%)	0	0	(0%)
	STOMATITIS	0	0	(0%)	1	1	(1.09%)
	VOMITING	4	4	(4.30%)	7	7	(7.61%)
Hemic & Lymphatic System	ANEMIA	5	5	(5.38%)	1	1	(1.09%)
	LYMPHADENOPATHY	1	1	(1.08%)	0	0	(0%)
	THROMBOCYTOPENIA	0	0	(0%)	2	1	(1.09%)
Metabolic & Nutritional Disorders	CREATININE INCREASED	0	0	(0%)	1	1	(1.09%)
	DEHYDRATION	2	2	(2.15%)	0	0	(0%)
	SGOT INCREASED	0	0	(0%)	1	1	(1.09%)
Nervous System	CONFUSION	0	0	(0%)	1	1	(1.09%)
	DIZZINESS	1	1	(1.08%)	0	0	(0%)
	NEURALGIA	1	1	(1.08%)	0	0	(0%)
	PERIPHERAL NEURITIS	1	1	(1.08%)	0	0	(0%)
	SOMNOLENCE	0	0	(0%)	1	1	(1.09%)
Respiratory System	BRONCHITIS	0	0	(0%)	1	1	(1.09%)
	COUGH INCREASED	1	1	(1.08%)	0	0	(0%)
	DYSPNEA	1	1	(1.08%)	0	0	(0%)
	EPISTAXIS	2	2	(2.15%)	0	0	(0%)
	PHARYNGITIS	2	2	(2.15%)	3	3	(3.26%)
	PNEUMONIA	2	2	(2.15%)	2	2	(2.17%)
	PULMONARY EMBOLUS	1	1	(1.08%)	0	0	(0%)
	RHINITIS	2	2	(2.15%)	2	2	(2.17%)
	SINUSITIS	1	1	(1.08%)	0	0	(0%)
Skin & Appendages	ACNE	1	1	(1.08%)	0	0	(0%)
	FURUNCULOSIS	0	0	(0%)	1	1	(1.09%)
	HERPES SIMPLEX	1	1	(1.08%)	2	2	(2.17%)
	HERPES ZOSTER	1	1	(1.08%)	1	1	(1.09%)
	MACULOPAPULAR RASH	2	2	(2.15%)	0	0	(0%)
	PRURITUS	2	2	(2.15%)	0	0	(0%)
	PUSTULAR RASH	1	1	(1.08%)	1	1	(1.09%)
	RASH	2	2	(2.15%)	0	0	(0%)
	SKIN DISORDER	1	1	(1.08%)	0	0	(0%)
	SWEATING	1	1	(1.08%)	1	1	(1.09%)
Skin & Appendages (cont'd)	URTICARIA	0	0	(0%)	1	1	(1.09%)
	VESICULOBULLOUS RASH	1	1	(1.08%)	0	0	(0%)
Special Senses	DEAFNESS	0	0	(0%)	1	1	(1.09%)
	EAR PAIN	1	1	(1.08%)	0	0	(0%)
	PHOTOPHOBIA	0	0	(0%)	1	1	(1.09%)
	TASTE LOSS	1	1	(1.08%)	0	0	(0%)
	TASTE PERVERSION	3	3	(3.23%)	1	1	(1.09%)

Body System	Preferred Term	Roxane (N = 93)			Mycelex® (N = 92)		
		X[2]	n[3]	(%[4])	X[2]	n[3]	(%[4])
Urogenital System	PENIS DISORDER	0	0	(0%)	1	1	(1.09%)
	URINARY TRACT INFECTION	1	1	(1.08%)	1	1	(1.09%)
	VAGINITIS	0	0	(0%)	2	2	(2.17%)

[1] Patients were included if they received at least one dose of drug.
[2]Total number of occurrences of the event among patients who received at least one dose of study medication.
[3]Total number of patients with at least one occurrence of the event among those who received at least one dose of study medication.
[4] Percent of patients in that treatment arm who received at least one dose of study medication, having at least one occurrence of the event.

Table VIII: Deaths On Study

Site #	Pt ID	Rx Arm	Date/ First Dose	Date/ Last Dose	Date of Death	Cause of Death	Relationship to Study Drug
104		Roxane	09/19/01	10/02/01		Probable pulmonary embolus	Not related
107		Mycelex®	06/07/01	06/16/01		Advanced HIV	Not related
108		Mycelex®	08/31/01	09/13/01		Bronchopneumonia	Not related
111		Mycelex®	08/29/01	09/04/01		Intracranial infection	Not related
112		Roxane	10/03/01	10/16/01		Atypical pneumonia	Not related
113		Roxane	09/29/01	09/30/01		Cardiac failure	Not related

Other Serious Adverse Events

Site #	Patient ID	RX Arm	Date First Dose	Date Last Dose Prior to Event	Adverse Events	Action Taken with Study Drug	Outcome	Relationship
101		Roxane	07/16/01	07/22/01	Tuberculous bronchopneumonia, tuberculous pericarditis	Temporarily discontinued	Recovered	Not related
101		Roxane	10/18/01	10/18/01	Pulmonary tuberculosis with dehydration	Temporarily discontinued	Recovered	Not related
102		Roxane	08/13/01	08/26/01	Disseminated miliary tuberculosis, anemia	None	Ongoing at last update	Not related
103		Roxane	10/04/01	10/17/01	Disseminated tuberculosis	None	Ongoing at last update	Not related
111		Mycelex®	08/29/01	09/04/01	Biliary colic	None	Unknown	Not related
113		Roxane	10/19/01	10/23/01	Vomiting	Drug permanently discontinued	Ongoing at last update	Not related

Reviewer's comments: *This reviewer agrees with the sponsor that the cause of death for six patients in this study was not likely related to the study drugs. The patient population identified in this study is diagnosed with HIV and some with advanced opportunistic infections. Due to the nature of the underlying HIV infection, these patients are at high risk for developing serious complications that can result in death. None of the deaths were caused by events that have been associated with clotrimazole therapy. The incidence of elevation of liver enzymes reported in this study is very low and below the 15% incidence reported in the innovator's approved labeling.*

Retention Samples

All unused drug supplies were to be returned to the investigator or appointed designee who is responsible for dispensing and collection of the drug supplies. However, according to the study report (vol. 1.1, p 97), the investigator was instructed to return all remaining clinical supplies to the sponsor after the completion of the study. The copy of the inventory record and the record of returned clinical supplies were returned to the sponsor.

Reviewer's Comments: *The OGD Draft Guidance for Industry: Handling and Retention of BA and BE Testing Samples, posted August 2002, recommends the site not to send the reserve samples back to the study sponsor to eliminate the possibility for sample substitution by the study sponsor.*

V. Formulation

Ingredients	Test (mg)	Reference[1]
otrimazole	10.00	10.00
(Dextrates, NF)		
Povidone USP		
(Modified Cellulose Gum)		
(Microcrystalline Cellulose, NF)		
Magnesium Stearate, NF		
Total Troche Weight (mg)	1000.00	1000.00

[1]COMIS (NDA 19-855)

The Regulatory Branch review indicates that all inactive ingredients are acceptable for filing. (vol. 1.1.)

VI. Findings of Division of Scientific Investigation (DSI) Report: 8/14/03

The DSI concluded that their findings of study CLO-0199 is acceptable for Agency review. However, 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. In addition, the inspector commented that patient #1038 (site 107) should be excluded from the evaluable population due to violation of protocol. This patient was using topical clotrimazole cream prior to enrollment (ongoing since 10/01) and continued to receive this medication during the study. The inspector also found that two patients (#1002, #1024) from site 101 had fungal culture positive on Day 15 and Day 21, but these results were inaccurately transcribed on the CRF.

Reviewer's Comments: *This reviewer also agrees that patient #1038 (site 107) should be excluded from the evaluable population. The fungal culture results of patients #1002 and 1024 from site 101 for day 15 and day 21 should be corrected to positive for the statistical analysis. Regarding bioequivalence testing sample issue, it is the sponsor's 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 the sponsor fails 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. The Final Rule requires that retention samples be randomly collected and retained from each shipment received by the clinical site.*

VII. Findings of Statistical Review: 11/26/03

The conclusion of the FDA statistical review failed to support the bioequivalence of the test and the reference products. The 90% CI of the clinical cure rate for the evaluable population at the primary endpoint did not fall within -0.20 and +0.20. The primary endpoint was evaluated based on clinical outcome at the 7-day follow-up visit (day 21).

Since the sponsor inappropriately discontinued a large portion of patients with positive fungal cultures at the end of treatment without regard to clinical status and designated them as clinical failures, this reviewer asked the FDA statistician to reevaluate the clinical outcome at the primary endpoint as discussed above.

After further exclusion of unevaluable patients that were inappropriately designated by the sponsor as failures, the 90% CI of the clinical cure rate in the evaluable population at the primary endpoint 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 support the bioequivalence. The summary of the FDA statistician's data is shown below.

Equivalence Analyses

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.**

VIII. Conclusion

The data presented in this ANDA failed to demonstrate that Roxane's Clotrimazole Troches, 10 %, is bioequivalent to the reference listed drug, Mycelex® Troche/Lozenge. The FDA statistical review confirms that the 90% CI of the proportional difference in clinical cure at the primary endpoint (7-day post treatment, day 21) did not fall within the limits of (-0.20, +0.20).

IX. Recommendation and comments to be conveyed to the sponsor

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). The sponsor 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 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. 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. Four patients that died during the study were also analyzed by the sponsor as treatment failures in the 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.

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

4. One patient that had a clinical response of cure on the Day 21 visit was excluded by the sponsor 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.

5. Three patients were analyzed 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 PP analysis.

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

7. After further exclusion of unevaluable patients that were inappropriately designated by the sponsor as clinical failures, the 90% CI of the clinical cure rate in the evaluable population at the primary endpoint 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.

8. 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 the sponsor's 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 the sponsor fails 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.

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

12/12/03
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12/17/03
Date

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

CC: ANDA 76-387
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 12/12/03
HFD-600/D. Hixon ORH 11/12/03
HFD-650/D. Conner 12/17/03

BIOEQUIVALENCY - UNACCEPTABLE

submission date:
March 28, 2002
July 17, 2003 (KS)

1. Bioequivalence Study (STU)

Strengths: 10 mg
Outcome: UC

2. Study Amendments (STA)

Strengths: 10 mg
Outcome: ~~**N/A**~~ UC (KS)

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

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

REVIEW OF RESPONSE TO DEFICIENCY LETTER

ANDA 76-387 Amendment
Drug Product: Clotrimazole Troche, 10 mg
Sponsor: Roxane Laboratories, Inc.
Reference Listed Drug: Mycelex® Troche/Lozenge (Bayer), NDA 18713
Reviewer: Carol. Y. Kim, Pharm.D.
Submission dates: 3/28/02; 7/17/03 & 9/16/03 (electronic datasets)
Date of Sponsor's Response to Deficiency Letter: February 17, 2004
Date of Review: March 24, 2004

V:/firmsnz/roxane/ltrs&rev/76387AM.0204.mor

History of ANDA 76-387

ANDA 76-387 for Clotrimazole Troche, 10 mg, was submitted by Roxane Laboratories, Inc. on 3/28/02. The application included a bioequivalence study with a clinical endpoint to establish bioequivalence between the test and reference products. OGD reviewed the bioequivalence study and found it inadequate to demonstrate bioequivalence. The sponsor discontinued a large number of patients (52) at the end of treatment because of positive fungal culture results (regardless of clinical status) and inappropriately designated them as treatment failures in the PP population analysis.

The primary endpoint for this product is a clinical response at the follow-up visit 7 days after completion of a 14-day course of therapy (day21). Standard of care does not require further systemic treatment for positive fungal cultures in the absence of clinical evidence of disease. All patients who had clinical evaluation of "cure" or "improved" at the end of treatment should have continued the study for an additional 7 days without further therapy and should have been evaluated for clinical cure at the 7-day follow-up visit (day 21). Any patient that developed worsening clinical signs and symptoms during that follow-up period should have been discontinued at the time of worsening and analyzed as a treatment failure. Instead, the sponsor discontinued all patients that had positive fungal culture results at the end of treatment without considering their clinical status. Therefore, in the OGD evaluation of those patients who were discontinued because of positive fungal cultures at the end of treatment, patients that had clinical evaluation of "cure" or "improved" at the end of treatment were considered as "unevaluable" and were excluded from the evaluable population. Patients that had worsening or new clinical signs and symptoms at the end of treatment were analyzed as treatment failures.

After excluding 43 patients that were considered as "unevaluable" patients, the study failed to meet the established bioequivalence criteria. The FDA statistical review indicated that the 90% CI of the difference in clinical cure rates between the test and reference products for the FDA evaluable population was (-21.2, 13.0). See statistical review dated 11/26/03 for details.

Based on the FDA statistical analysis, the study failed to demonstrate bioequivalence of the test and the reference products. The OGD notified the sponsor of this deficiency on January 8, 2004 and provided further clarification on January 22, 2004.

Roxane's response to the deficiency letter

On February 17, 2004, the sponsor submitted a point-by-point response to the Agency's deficiency letter dated January 22, 2004. The sponsor does not agree with the Agency's decision that their study failed to demonstrate bioequivalence of their product to the reference product. The sponsor also submitted additional data for four patients that were not previously included in database for the original ANDA submission.

Upon the review of the sponsor's itemized responses, this reviewer's point-by-point comments are listed as follows:

Roxane's Response #1:

The sponsor claims that those 52 patients were not inappropriately discontinued because they were discontinued according to the original study protocol criteria. Section 5.4 of the original protocol included a specific section of "Reasons for early patient termination from the study (prior to day 21 visit) and the third bullet point states "Positive fungal culture of the oropharynx at day 15 evaluation (which would presumably require systemic antifungal therapy)." Despite multiple communications between the OGD and the sponsor regarding the study design, the sponsor argues that the OGD did not provide adequate detailed information. The sponsor states that the OGD did not recommend that patients should not be terminated from the study at day 15 in the presence of a positive fungal culture as clearly indicated in their original protocol. The sponsor summarized previous communication letters with the OGD from January 6, 2000 to September 18, 2000 to support their belief that the OGD did not provide a clear recommendation that they should not terminate patients from the study at day 15 because of a positive fungal culture as stated in Section 5.4 of the protocol.

Reviewer's Comment #1:

The sponsor's original protocol #CLO-0199 was reviewed by the OGD medical officer on February 28, 2000. In this protocol, the sponsor proposed the primary endpoint comparing the incidence of negative fungal cultures of the oropharynx after 14 days of treatment in the intent-to-treat population. In the OGD response, P00-001 (3/21/00), Roxane was informed that the acceptable primary endpoint is a total cure (both clinical cure and mycological cure) at day 15 and that a placebo-controlled study is required.

In reference to the OGD's comments (P00-001), the sponsor argued on March 29, 2000 that the demonstration of clinical equivalence should be sufficient for the approval of their product without including a placebo arm since the efficacy of clotrimazole for the treatment of oral candidiasis is well established.

After further discussion of Roxane's original protocol with the Division of Dermatologic and Dental Drug Products (DDDDP) and Division of Special Pathogen & Immunological Drug Products, the OGD informed the sponsor on June 22, 2000 that the placebo group is not necessary and the primary efficacy assessment should be the clinical outcome at approximately 7 days post therapy. This comment was provided to replace the advice given in the previous letter. Furthermore, the OGD clarified that patients should be treated for a total of 14 days and should

be assessed for the efficacy endpoints 7 days after the end of treatment. (See P00-001B dated 7/31/00)

In a subsequent e-mail communication between the Division of Bioequivalence (Lizzie Sanchez) and Roxane (Elizabeth Ernest) on August 11, 2000, Roxane indicated that they plan to modify their clinical endpoint study. The sponsor's proposed primary endpoint was changed to the percentage of patients with a negative fungal culture of the oropharynx at Day 21 in the intent-to-treat population. In this e-mail, the sponsor noted that the day 21 evaluation will be considered the follow-up and the final visit for the study.

OGD responded on September 18, 2000 (P00-001C) that the primary endpoint is the clinical response at the Day 21 in the evaluable population after completion of 14 days of treatment and not the fungal culture result in the Intent-to-Treat Population. The OGD explained that the clinical response is chosen because it is the disease manifestation and fungal culture of the oropharynx does not always correlate with clinical response.

Based on the OGD comments, the sponsor amended their original protocol and incorporated the primary endpoint to be the clinical response at the 7-day follow-up visit (day 21). The sponsor replaced the final visit from originally proposed day 29 (post 2 week follow-up visit) visit to day 21, but maintained the statement that only patients that had completed the treatment and had a negative fungal culture of the oropharynx at the end of treatment visit will return for the follow-up visit in the protocol. The amended protocol was not submitted to OGD for review prior to this ANDA submission.

Since the OGD did not accept the primary endpoint originally proposed by the sponsor, all subsequent communications were provided to the sponsor to clarify the accepted primary endpoint and to facilitate further modification of their protocol based on the OGD's comments. It is the sponsor's responsibility to incorporate necessary changes in the protocol to be consistent with the OGD recommended primary endpoint. Therefore, the OGD disagrees with the sponsor's position that the OGD has not provided clear advice on the development of their final protocol.

Roxane's Response #2:
Six patients that had positive fungal culture results with absent clinical signs and symptoms at the end of treatment visit returned for the day 21 visit, and OGD included them in the evaluable population, using the day 21 data. The sponsor agrees with this decision.

Reviewer's comment #2:
The sponsor's response is acceptable.

Roxane's Response #2b:
Nine patients that had both a positive fungal culture and clinical failure (no improvement in signs and symptoms of oral candidiasis) at the end of treatment were included by OGD in the evaluable population as treatment failures. The sponsor agrees with this decision.

Reviewer's comment #2b:
The sponsor's response is acceptable.

Roxane's Response #2c:
OGD excluded patients that were discontinued for positive fungal culture results with clinical outcome of "cure" or "improved" at the end of treatment from the evaluable population. The sponsor argues that they should not be unevaluable because they met the evaluability criteria established in the protocol as discussed above.

Reviewer's comment #2c:
OGD disagrees with the sponsor's rationale for designating these patients as treatment failures. The appropriate changes should have been incorporated into the protocol to assure that the design of the study will support accurate evaluation of the primary endpoint.

Roxane's Response #3:
Four patients died during the study due to conditions unrelated to the study drug. OGD excluded them from the per protocol population. The sponsor argues that they met the protocol defined criteria for inclusion in the evaluable population and should be analyzed as treatment failures.

Reviewer's comment #3:
Since there is no data to support that these 4 patients' deaths were related to treatment failure, the OGD disagrees with the sponsor's decision to analyze them as treatment failures.

Roxane's Response #4:
The sponsor agrees with the OGD's position to exclude one patient who was not randomized into the study from the evaluable population.

Reviewer's comment #4:
The sponsor's response is acceptable.

Roxane's Response #5:
The sponsor excluded one patient that had a clinical response of cure on the day 21 visit from the per protocol population because fungal culture was not performed on day 15. OGD included this patient in the evaluable population as a treatment success but excluded the patient from the day 15 secondary endpoint of mycological response. The sponsor agrees with this decision.

Reviewer's comment #5:
The sponsor's response is acceptable.

Roxane's Response #6:
The sponsor disagrees with the OGD's decision to exclude three patients from the evaluable population because they discontinued the study due to adverse events. They were analyzed by the sponsor as treatment failures because they did not have the data required to establish cure. Two of the three had only a baseline visit, and the other had only baseline and Day 8 visits. None of the patients completed 14 days of treatment. The sponsor argues that exclusion of these

patients is inappropriate because they met the protocol defined criteria for the evaluable population.

Reviewer's comment #6:
The OGD disagrees with the sponsor's decision to include them as treatment failures when they were discontinued by the sponsor due to adverse events. In the summary dataset, "pat_sum.xpt", provided by the sponsor on February 16, 2003, the sponsor indicated that the reason for discontinuation was due to adverse event, severe vomiting, and an allergic reaction. These patients discontinued the study due to adverse events, non-compliance, lost to follow-up or death not related to treatment effect and should not be analyzed as treatment failures.

Roxane's Response #7:
The sponsor agrees with the OGD's decision to exclude one patient that received topical clotrimazole during the study. This patient was originally included in Roxane's evaluable population.

Reviewer's comment #7:
The sponsor's response is acceptable.

Roxane's Response #8:
After including and excluding the patients recommended by the OGD beginning with the 147 per protocol patients from the original submission, the sponsor identified a total of 97 patients that were considered as evaluable. Based on the sponsor's analysis, the 90% CI meets the bioequivalence criteria (-19.3%, 14.1%). The sponsor's data analyses for the primary and secondary endpoints are provided in details.

Reviewer's comment #8:
As discussed above, the OGD disagrees with the sponsor's decision to include patients without data for the primary endpoint in the evaluable population as treatment failures. The FDA statistician identified a total of 136 patients qualified for evaluable population prior to performing additional 43 exclusions that were considered as "unevaluable" patients. The sponsor's identified 97 evaluable patients included four patients that were either not treated or did not return for at least one post-baseline visit. Per protocol, these four patients (T: 104-1005, 101-1009; R: 110-1001, 101-1015) should be excluded from the evaluable population.

Roxane's Response #9:
Using the OGD's recommended statistical method, the 97 FDA-defined evaluable population identified by the sponsor meets the bioequivalence criteria (-19.3%, 14.1%).

Reviewer's comment #9:
Based on the 94 FDA-defined evaluable population from the statistical review of 11/26/03, the 90% CI of the difference in clinical cure rate between the test and reference products was determined to be (-21.2, 13.0).

Roxane's Response #10:
The sponsor has identified four additional patients who had positive fungal culture results with absent clinical signs and symptoms at Day 15, but still returned for their Day 21 visit. The Day 21 CRFs for these 4 patients were lined through, dated, and initialed as visits completed in error per protocol. These data were not entered into the database but are available in the CRFs (previously submitted) to allow analysis according to the Day 21 clinical response data. The four patients are as follows: 102-1008, 102-1012, 102-1014, and 103-1017.

When the sponsor includes these four patients into the evaluable population, the 90% CI meets the bioequivalence criteria (-18.9, 13.8) according to the sponsor's analysis.

Reviewer's comment #10:
The OGD agrees that the 90% CI of the difference in clinical cure rates between the test and the reference products meets the bioequivalence criteria after including these four additional patients into the evaluable population. After reviewing the CRFs for these patients, this reviewer confirmed that these four patients had Day 21 visit data. Their clinical responses at the Day 21 visit are as follows:

102-1008 (R): Absent/Cure *102-1014 (T): Absent/Cure*
102-1012 (T): Absent/Cure *103-1017 (R): Absent/Cure*

This reviewer also checked the CRFs for the rest of the patients that were initially considered as evaluable but excluded for missing Day 21 data and did not find any more Day 21 clinical response data.

Following review of the CRFs for these patients and the FDA statistical review (11/26/03), this reviewer identified a new FDA evaluable population of 97 patients. One patient (#1003) in the test group that was previously carried forward by the FDA statistician as a treatment failure should have been designated as "unevaluable" and excluded based on the review of clinical data. Based on the adjusted number of clinical cures (37 in the test and 36 in the reference) in this new evaluable population of 97 patients, the 90% CI for the difference in clinical cure rates between the test and the reference products meets the bioequivalence criteria (-0.19, 0.13). The FDA statistician confirmed these 90% CI calculations (see attachment for details).

After incorporating the above changes in the evaluable population, the 90% CI of the difference in clinical cure rates between the test and reference products is within the established limits of (-.20, +.20) and the study is therefore adequate to demonstrate bioequivalence of Roxane's product to the reference listed drug (RLD).

Roxane's Response #11:
The sponsor states that the patient evaluability was defined clearly in their protocol under Section 8.3. Based on the FDA's deficiency comments, the sponsor believes that the FDA has applied criteria other than those stated in their final protocol. Section 8.3 of their protocol states that "patients are evaluable for efficacy if they: 1) received at least 50% of the prescribed study medication during the 14 day treatment period, as assessed primarily by troche count and

secondarily by patient interview (if troche count is not available); 2) had a fungal culture of the oropharynx at baseline that was positive for Candida species; 3) had no major protocol violations; and 4) did not withdraw from the study prematurely (prior to Day 21) for reasons other than adverse events or treatment failure. The sponsor wants to know if the OGD applied the same criteria as proposed by their protocol. If the OGD does not agree with their analysis based on the new information provided in this amendment, the sponsor requests a list of all patients that the FDA has included/excluded for the analysis.

Reviewer's comment #11:
Based on additional data provided with the current submission, the OGD agrees that the sponsor's study is adequate to demonstrate bioequivalence of Roxane's product to the RLD.

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

Recommendation
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 the sponsor's 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.

After reviewing the additional four patients' data provided by the sponsor with the current submission, the 90% CI of the difference in clinical cure rates between the test and reference products at Day 21 is within the established limits of (-0.20, +0.20) and the study is therefore adequate to demonstrate bioequivalence of Roxane's product to Mycelex® Troche, 10 mg.

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

In the future the sponsor is strongly advised to submit an amended protocol for review prior to conducting a bioequivalence study for an ANDA when the original protocol requires a significant change in study design based on the OGD recommended primary endpoint. It is the sponsor's responsibility to assure that the study design is appropriate and data provided by the sponsor will support accurate analysis of the accepted primary endpoint.

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

3/24/04
Date

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

3/24/04
Date

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

5/3/04
Date

Attachment

I concur with Helen's calculations.

Don Schuirmann

-----Original Message-----
From: Li, Huaixiang
Sent: Wednesday, March 03, 2004 4:36 PM
To: Kim, Carol Y
Cc: Machado, Stella G; Schuirmann, Donald J; Hixon, Dena R
Subject: RE: Confirmation requeted on new data for ANDA 76-387 (Clotrimazole Troche)

Carol,

The 90% CI for new outcome is (-19.1, 13.9) for test=74%(37/50) and reference=76.6%(36/47) based on your update information.

Helen

-----Original Message-----
From: Kim, Carol Y
Sent: Wednesday, March 03, 2004 4:09 PM
To: Li, Huaixiang
Cc: Machado, Stella G; Schuirmann, Donald J; Hixon, Dena R; Kim, Carol Y
Subject: Confirmation requeted on new data for ANDA 76-387 (Clotrimazole Troche)

Helen,

We need your help to confirm the 90% CI based on new information submitted by the sponsor for ANDA 76-387 (Clotrimazole Troche, Roxane).

This is a study that the sponsor inappropriately discontinued a large number of patients that were considered clinical cure at the end of treatment (day 15) based on positive culture result. Since the primary endpoint is a clinical response at the follow-up visit, all patients that were considered clinically better at the end of treatment should have continued the study up to the follow-up visit (day 21) and not discontinued based on positive culture result. Because the sponsor inappropriately discontinued and classified them as "treatment failure", we asked you to change them as "unevaluble" and exclude from the PP population analysis.

Based on our comments, those patients that had positive culture but were considered clinically "improved" or "cure" at the end of treatment visit were classified as "unevaluable" and were excluded from the PP population analysis. Those patients that had positive culture at the end of treatment visit but were considered clinical failure at the end of treatment were included in the PP population analysis as treatment failure.

Based on our PP population analysis, the sponsor's study did not meet 90%CI (-21.2, 13.0) for clinical cure at day 21 (primary endpoint) and we sent the deficiency to the sponsor.

On February 17, 2004, the sponsor submitted additional data that they have discovered from the CRF. The sponsor claims that four patients that we originally excluded due to "unevaluable" had data for the day 21 in the CRF. Based on their submitted information, four more patients from the "unevaluable" category will be considered as clinical cure (2 in the test and 2 in the reference group) at the primary endpoint (day 21). One patient (test) that was originally carried forward as "failure" in your statistical analysis is considered "unevaluable" and should be excluded from the PP population.

Based on your "summary of equivalence analysis" from the statistical review dated 11/26/03 (page 6), day 21 result is as follows:

Test: 35 (cure)/49
Ref: 34 (cure)/45

If we add above mentioned patients to the PP population and exclude one patient that was originally carried forward as treatment failure from the test group, the PP population changes to the following:

New PP population
Test: 37 (cure)/50; 13 failure
Ref: 36 (cure)/47; 11 failure

Based on my preliminary analysis, the 90% CI is (-0.19, 0.13). Can you please confirm the 90% CI based on the updated (new) PP population?

Thanks
carol

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

CC: ANDA 76-387
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
HFD-600/D. Hixon 3/24/04
HFD-650/D. Conner 5/3/04

BIOEQUIVALENCY - ACCEPTABLE

submission date:
February 17, 2004

1. Study Amendment (STA)

Strengths: 10 mg
Outcome: AC

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-387 Amendment SPONSOR : Roxane Laboratories

DRUG AND DOSAGE FORM : Clotrimazole Troche, 10 mg

STRENGTH(S) : 10 mg

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable pending acceptable response to deficiency comment regarding the dissolution method.

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status: completed on 8/14/03	Inspection results: acceptable
First Generic _____ New facility _____ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

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

INITIAL : Carol Y. Kim DATE : 3/24/04

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

INITIAL : Dena R. Hixon MD DATE : 3/24/04

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

INITIAL : _____ DATE : 5/3/04

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-387
Drug Product Name	Clotrimazole Troche
Strengths	10 mg
Applicant Name	Roxane Laboratories, Inc.
Address	1809 Wilson Road, Columbus, OH 43228
Submission Date(s)	March 10, 2004 (original submission March 28, 2002; acceptable for filing March 29, 2002)
Amendment Date(s)	~~March 26, 2004~~ (telephone amendment) April 1, 2004
Reviewer	Sheryl D. Gunther
First Generic	Potential First Generic
File Location	V:\firmsnz\roxane\ltrs&rev\76387A0304.doc

REVIEW OF AN AMENDMENT

I. Executive Summary

This drug product requires a BE study with clinical end points. On 3/28/2002, Roxane submitted a BE study with clinical end points. Carol Kim and Dena Hixon found the study deficient (see V:\firmsnz\roxane\ltrs&rev\76387A.mor0302.doc). The firm responded to the deficiencies 2/17/2004, and the clinical endpoint study was found to be acceptable pending a response to the deficiency comment regarding the dissolution method (see V:\firmsnz\roxane\ltrs&rev\76387AM.0204.mor.doc).

Since there is no USP or FDA dissolution testing method for this drug product, the DBE sent a deficiency letter on 2/12/2004 to the firm advising it to develop a dissolution testing method. In this amendment, the firm has submitted a response to this bioequivalence deficiency letter. The firm has included a dissolution method development report, including (1) a pH solubility profile of the drug substance; (2) studies of agitation speed and media volume; (3) dissolution data obtained under the conditions found to be optimal based on (1) and (2); (4) two certificates of analysis for the dissolution profile data (one obtained under the optimal testing conditions and the other using a higher pH media with larger volume); (5) a revised drug product specification identifying the optimal dissolution method; and (6) an updated stability report including dissolution data. However, the firm did not submit the comparative dissolution testing data. Pursuant to a telephone amendment (March 26, 2004), the firm has provided comparative dissolution data for 12 units of their product and the reference-listed drug (RLD), Bayer Pharmaceuticals Corporation Mycelex® (clotrimazole) troches, 10 mg, obtained under the testing conditions deemed optimal (Apparatus II @ 50 rpm, 500 mL of 0.1N HCl). The dissolution method and comparative dissolution data are found to be acceptable; however, the Division of Bioequivalence (DBE) does not agree with the firm's proposed dissolution specification (NLT — % (Q) in 60 minutes) and recommends the dissolution specification be revised (NLT —% (Q) in 45 minutes).

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Clotrimazole Troche, 10 mg
Reference Product	Mycelex® (clotrimazole) Troche, 10 mg
RLD Manufacturer	Bayer Pharmaceuticals Corporation
NDA No.	18-713
RLD Approval Date	June 17, 1983
Background*	Clotrimazole is a synthetic broad-spectrum antifungal agent that inhibits the growth of pathogenic yeasts. The troche dosage form is a large, slowly dissolving tablet (lozenge) for topical use in the mouth. For the topical treatment of oropharyngeal candidiasis, the usual dosage of oral clotrimazole is one 10-mg lozenge 5 times daily for 14 consecutive days. For prophylaxis to reduce the incidence of oropharyngeal candidiasis in patients who are immunocompromised as the result of immunosuppressive therapy (e.g., corticosteroids, antineoplastic agents, radiation therapy), the usual dosage of oral clotrimazole is one 10-mg lozenge 3 times daily for the duration of chemotherapy or until corticosteroid therapy is reduced to maintenance levels. After oral administration of a 10 mg clotrimazole troche to healthy volunteers, clotrimazole concentrations persist in saliva for up to three hours following the approximately 30 minutes needed for a troche to dissolve. The long term persistence of drug in saliva appears to be related to the slow release of clotrimazole from the oral mucosa to which the drug is apparently bound. Clotrimazole is also available as a cream, lotion, topical solution and vaginal tablets.

***References**:*

(1) AHFS Drug Information® (2004) Online by the American Society of Health-System Pharmacists, Inc., http://www.ahfsdruginformation.com
(2) DrugDex® Drug Evaluations, entry for Clotrimazole last revised

3/2002.; accessed via Micromedex online; http://csi.micromedex.com
(3) Martindale - The Complete Drug Reference - Monographs, copyright 1982-2004.; accessed via Micromedex online; http://csi.micromedex.com
(4) USP DI® Drug Information for the Health Care Professional – 24th Ed. (2004) Online, accessed via STAT!Ref (http://online.statref.com)

Relevant OGD/DBE History

The OGD has not approved any ANDAs for Clotrimazole Troche products. The DBE has reviewed the following protocols and controlled documents for generic formulations of Clotrimazole Troches, as well as the following ANDA submission for Clotrimazole Vaginal Tablets. Relevant history follows:

Protocols:

- USP monograph for Clotrimazole Troches (USP 24) specifies an *in vitro* disintegration test using buccal tablet methodology; firms should conduct comparative testing using this method.

99-005: Roxane Laboratories, submission date 2/12/1999

- USP monograph for Clotrimazole Troches (USP 23, Supplement 2) specifies an *in vitro* disintegration test using buccal tablet methodology; firms should conduct comparative testing using this method.

Controlled Document:

- No compendial or NDA dissolution method exists
- USP recommends disintegration testing using buccal tablet methodology; DBE does not accept disintegration tests for generic products
- DBE accepted the following method of *in vitro* testing for Clotrimazole ***Vaginal Tablets***:

  Medium: 900 mL 0.1 N HCl
  Apparatus: Paddle at 50 rpm
  Sampling: 10, 20, and 30 minutes
  Specifications: NLT (Q) —% in 30 minutes

The same method may be recommended for Clotrimazole Troches except for a higher speed and longer sampling time due to the large size and slow dissolving nature of the troches, along with additional testing in other media using a basket or paddle apparatus at different speeds. (See attached email correspondence provided in this controlled document in Appendix IV B of this review.)

- The firm should develop an *in vitro* dissolution testing method using the following conditions:

  Media: Water; 0.1 N HCl; Acetate Buffer, pH 4.5; and Phosphate Buffer, pH 6.8.

Volume: 900 mL
Apparatus: Basket at 100 rpm and Paddle at 50, 75, and 100 rpm
Sampling: 10, 20, 30, 60, and 90 minutes or until —% of the labeled amount is dissolved.

Specifications to be recommended based on comparative dissolution profiles of the test and reference formulations.

98-333: Paddock Laboratories, Inc., submission date 9/15/1998

- The present *in vitro* test (disintegration test) is not capable of detecting differences and variabilities between lots or batches; an *in vitro* dissolution test (**not disintegration**) is recommended.

Reviewer's Note: *Paddock Laboratories, Inc. submitted an extension stability protocol to support an ongoing clinical trial in an SOP (#00A-0016 Rev. 002) dated 10/24/2001. The protocol notes a dissolution test and specification among the stability tests, but does not indicate dissolution methodology. (Controlled Document #01-612; submission date 12/18/2001)*

- An *in vitro* dissolution test (**not a disintegration test**) is recommended.

ANDA: (Clotrimazole *Vaginal Tablets*, 100 mg)

73-249: Copley, submission dates 3/13/1992, 4/27/1993, and 5/17/1996.

- *In vitro* testing method found acceptable for Clotrimazole Vaginal Tablets:

Medium: 900 mL 0.1 N HCl
Apparatus: Paddle at 50 rpm
Sampling: 10, 20, and 30 minutes
Specifications: NLT (Q) — % in 30 minutes

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
In vitro dissolution	Yes	N/A
Waiver requests	No	--
Failed Studies	No	--
Amendments	Yes	1

C. Firm's Responses to Deficiencies

Deficiency # 1:

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.***

Firm's Response to Deficiency #1:

In developing an *in vitro* dissolution testing method, the firm reports the results of the following studies used to determine the dissolution characteristics of clotrimazole:

(1) **The pH-solubility profile of clotrimazole in media with a pH range of 1.0 to 8.0.**

The firm provided the following background:
(a) The solubility of clotrimazole in water at 25°C is 1×10^{-6} g/mL.
(b) Roxane has data demonstrating clotrimazole solubility to be 2×10^{-5} g/mL in 0.1N HCl at 37°C, with one hour of mixing.

The firm has chosen five times this amount ($5 \times (2 \times 10^{-5}) = 1 \times 10^{-4}$ g/mL) to study the solubility of clotrimazole in order to determine if the system approximates sink

conditions. Three replicate determinations for each media were done. Results were reported as follows:

Solubility Profile (mg/mL)						
pH	**Media**	**Sample 1**	**Sample 2**	**Sample 3**	**Average**	**% RSD**
1.0	0.1 M Hydrochloric Acid solution	0.106	0.106	0.106	0.106	0.5
4.5	Acetate Buffer	0.0105	0.0098	0.0116	0.0106	8.6
6.5	Phosphate Buffer	0	0	0	0	--
8.0	Phosphate Buffer	0	0	0	0	--

Firm's Conclusions: The firm notes that as pH increased, solubility decreased significantly until the compound was essentially insoluble at pH 6.5. The firm concludes that clotrimazole is only soluble in low pH media, such as 0.1 N hydrochloric acid solution.

(2) **Dissolution-test method parameters for rotational speed and volume.** An experimental design with three replicate determinations for each experiment was done. Dissolutions were performed in 0.1 N HCl media, and three tablets were tested at each condition. Speeds studied were 50, 75, and 100 RPM; volumes studied were 500, 700, and 900 milliliters. Samples were pulled at 10, 15, 30, 45, and 60 minutes. Results were reported as follows:

Experimental Design for Dissolution Parameters						
RPM	**Volume**	**10 min**	**15 min**	**30 min**	**45 min**	**60 min**
50	**500**	34	52	91	107	108
50	**900**	40	59	101	106	109
100	**500**	60	80	111	109	109
100	**900**	76	91	103	107	104
75	**500**	48	69	105	104	108
75	**900**	55	77	105	102	108
50	**700**	33	54	89	106	103
75	**700**	52	73	103	101	104
50	**700**	39	61	96	104	105
100	**700**	71	81	107	101	105

Firm's Conclusions: The firm concluded that the conditions of 50 RPM and 500 mL of 0.1 N HCl produced reasonable release rates with minimal agitation and with a volume of media approximating sink conditions.

(3) **Dissolution Profile.** Based on the above results, the firm determined the optimal test method conditions to be the following:

Apparatus: USP 2 (Paddles)
Media: 0.1 N HCl
Volume: 500 mL
Rotational speed: 50 rpm
Temperature: 37.0° ± 0.5° C

Using this method, the dissolution results were reported as follows. The firm provided data for only 6 tablets.

Sampling Time (minutes)	Roxane Laboratories' Clotrimazole Troche, 10 mg Lot No. 019011		
	Mean	%RSD	Range*
10	34%	7.9	
15	53%	7.0	
30	90%	4.4	
45	107%	4.3	
60	106%	2.7	

* Reviewer-calculated data; the firm provided standard deviation but did not calculate the range.

(4) The firm has provided Certificates of Analysis for their product, Clotrimazole Troche, 10 mg, Lot # 019011, with dissolution profile data. Certificates were provided for two testing methods considered to be optimal: the method shown above with 500 mL of 0.1 N HCl, and with 900 mL of pH 4.5 Acetate Buffer. Results are as follows:

Certificate of Analysis Percent Dissolved: Clotrimazole Troche, 10 mg (Lot # 019011; Date of Manufacture: 02/2001)			
Apparatus: USP 2 (Paddles) **Media:** 0.1 N HCl **Volume:** 500 mL **Rotational speed:** 50 rpm **Temperature:** 37° ± 0.5° C			
Sampling Time (minutes)	**Mean**	**%RSD**	**Range**
10	33	9.6	
15	52	6.3	
30	91	3.3	
45	103	4.9	
60	102	4.1	

Certificate of Analysis Percent Dissolved: Clotrimazole Troche, 10 mg (Lot # 019011; Date of Manufacture: 02/2001)			
Apparatus: USP 2 (Paddles) **Media:** Acetate Buffer, pH 4.5 **Volume:** 900 mL **Rotational speed:** 50 rpm **Temperature:** 37° ± 0.5° C			
Sampling Time (minutes)	**Mean**	**%RSD**	**Range**
10	12	6.6	
15	25	11.9	
30	48	6.9	
45	65	2.2	
60	73	1.2	

(5) The firm has revised its Drug Product Specification No.1278-05 for Clotrimazole Troche, 10 mg, (effective date March 9, 2004) by removing the disintegration test and adding the dissolution test.

The method added is the following, based on the conditions found to be optimal in the above studies:

Apparatus: USP 2 (Paddles)
Media: 0.1 N HCl
Volume: 500 mL
Rotational speed: 50 rpm
Temperature: 37° ± 0.5° C

The specification is noted to be:

NLT —% (Q) of the labeled amount dissolves in 60 minutes.

(6) An updated stability report for the product is provided, which includes dissolution testing data using the method noted above that has been included in the revised Drug Product Specification No. 1278-05. All dissolution test results throughout the period reported were observed to conform to the specification limit of Q = —% of the labeled amount dissolved in 60 minutes.

Reviewer's Comment: *The reviewer notes that the stability data only indicate a mean value and range determined at 60 minutes for each stability time point; no intermediate values are reported for sampling times under 60 minutes.*

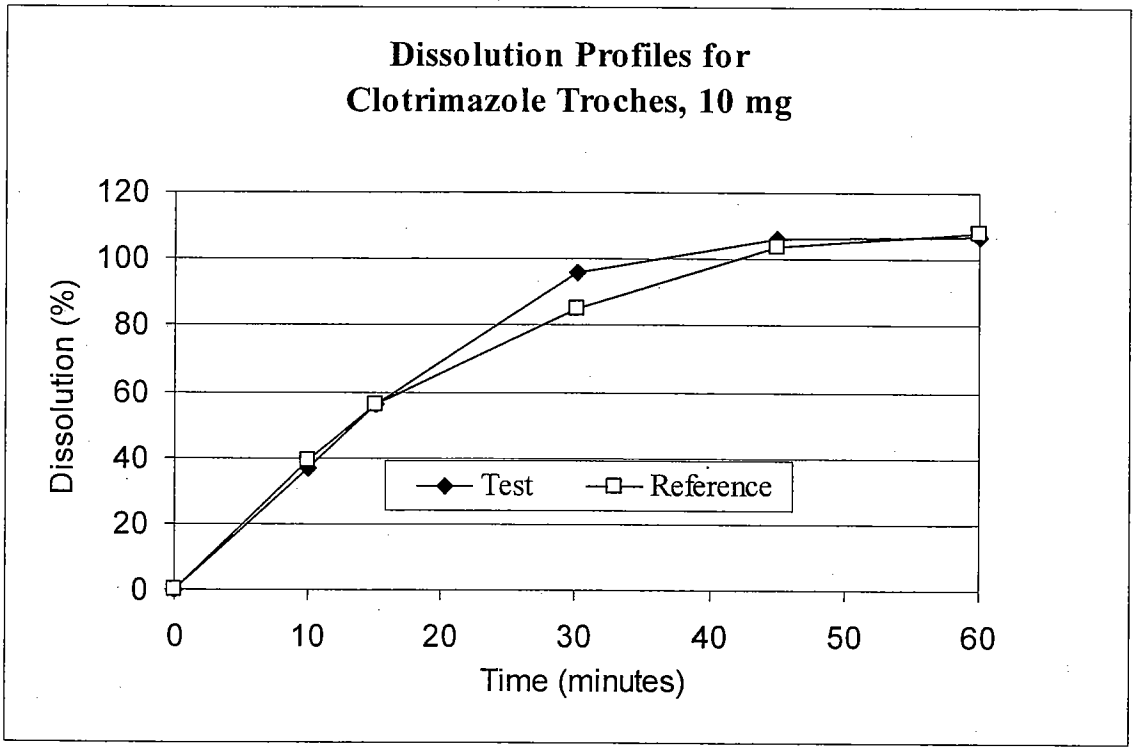
Comparative Dissolution Data in Response to Telephone Amendment:

In response to a telephone amendment (March 26, 2004), the firm provides the following comparative dissolution data.

Method:

Apparatus:	USP 2 (Paddles)
Media:	0.1 N HCl
Volume:	500 mL
Rotational speed:	50 rpm
Temperature:	37° ± 0.5° C

Sampling Time (minutes)	Test Product ROXANE Clotrimazole Troche, 10 mg Lot No. 019011			Reference Product BAYER Mycelex® Troche, 10 mg Lot No. 9DFP		
	Mean	%CV	Range	Mean	%CV	Range
10	37%	8.3		39%	17.4	
15	56%	8.2		56%	15.2	
30	96%	4.8		85%	8.5	
45	106%	2.1		104%	3.8	
60	107%	2.3		108%	2.7	



D. Reviewer Comments

The reviewer finds the *in vitro* dissolution method (Paddles @ 50 RPM, 500 mL of 0.1 N HCl) developed by the firm for its Clotrimazole Troches, 10 mg, to be acceptable. The comparative dissolution testing of its product to the reference-listed drug (RLD), Bayer Corporation's Mycelex® (clotrimazole) Troches, 10 mg, using this method, is acceptable. Based on the data, the reviewer does not agree with the firm's proposed specifications of NLT – % (Q) in 60 minutes and recommends changing the dissolution specifications to NLT – % (Q) in 45 minutes.

E. Deficiency Comment

The Division of Bioequivalence (DBE) does not agree with the firm's proposed dissolution specifications of NLT —% (Q) in 60 minutes and recommends changing the dissolution specifications to NLT —% (Q) in 45 minutes.

F. Recommendations

The Division of Bioequivalence recommends changing the dissolution specifications to NLT —% (Q) in 45 minutes.

The firm should be informed of the above deficiencies and recommendations.

Sheryl D. Gunther 4/23/2004

Sheryl D. Gunther, Pharm.D., Reviewer, Branch I Date

4/23/2004

Shriniwas G. Nerurkar, Ph.D., Team Leader, Branch I Date

for Barbara M. Davit 4/23/04

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

CC: ANDA #76-387, original, HFD-652 (Gunther), Drug File, Division File

IV. Appendix

A. Formulation

The formulations for the test and reference products of Clotrimazole Troche, 10 mg, are shown below.

Ingredient	Test* Roxane Laboratories' Clotrimazole Troche, 10 mg ANDA # 76-387	Reference** Bayer Corporations' Mycelex® (clotrimazole) Troche, 10 mg NDA # 18-713
	mg per tablet	
Clotrimazole, USP	10.00	10.00
[redacted] (Dextrates, NF)	[redacted]	[redacted]
Povidone USP [redacted]	[redacted]	[redacted]
[redacted] (Modified Cellulose Gum)	[redacted]	--
Magnesium Stearate, NF [redacted]	[redacted]	[redacted]
[redacted] (Microcrystalline Cellulose, NF)	[redacted]	[redacted]
Total Troche Weight	**1000.00**	**1000.00**

* Obtained from Roxane Laboratories' Stability Experience Report No. ROX SP-1267-AN-AO-AP-AQ-02-03, for Clotrimazole Troche, 10 mg, Lot #019011, page 4 (dated March 11, 2004). The reviewer verifies this formulation to be the same as that provided in the CMC Review for ANDA #76-387, review date 10/24/2002.

** Obtained from COMIS Database (NDA 18-713); also referenced in Bioequivalence Review of a Clinical Endpoint Study (ANDA #: 76-387; review date 12/12/2003; V:\firmsnz\roxane\ltrs&rev\76387A.mor0302.doc)

B. Additional Attachments

Attachment I. The following is an e-mail correspondence pertaining to the dissolution method for Clotrimazole Troches. The correspondence is provided as an attachment in Controlled Correspondence # [redacted] submission date [redacted].

-----Original Message-----
From: Tran, Nhan L
Sent: Monday, September 30, 2002 3:31 PM
To: Gokhale, Mamata S
Cc: Singh, Gur J P
Subject: RE: Dissolution method for clotrimazole Troche/lozenge, 10 mg
Sensitivity: Confidential

Yes as we have discussed.
Thanks,

-----Original Message-----
From: Gokhale, Mamata S
Sent: Monday, September 30, 2002 3:30 PM
To: Tran, Nhan L
Cc: Singh, Gur J P
Subject: Dissolution method for clotrimazole Troche/lozenge, 10 mg
Sensitivity: Confidential

Tran,

I have a control document asking for a dissolution method for this product. Currently there is only disintegration test and no compendial dissolution method. I found one of your old reviews on clotrimazole vaginal tablets recommending 0.1N HCl and paddle at 50 rpm. Considering this, I will ask the firm to use water, 0.1N HCl and buffers, pH 4.5 (Acetate) and 6.8 (Phosphate) with paddle at 50, 75 and 100 rpm and basket at 100 rpm. The RLD is marketed as large slow dissolving tablets. So it would be appropriate to recommend sampling up to 90 minutes or until —% of the labeled amount is released. Do you agree?

Mamata

Attachment II. The following email correspondences are confirmations sought by the reviewer regarding the DBE's recommendations relative to the firm's proposed dissolution methodology and specifications.

From: Davit, Barbara M
To: Tran, Nhan L; Gunther, Sheryl
Cc: Nerurkar, Shriniwas G; Conner, Dale P
Subject: RE: ANDA 76-387 Clotrimazole Troches, 10 mg (Roxane)

Nhan:

I concur with your recommendation, based on the following observations:

(1) On 3/5/03, the dissolution range for Roxane's Clotrimazole Troche 10 mg (12 troches) was ——— %.

(2) On 4/1/03, the range was ——— %.

The product should meet the specifications that you recommend.

I talked to Dale about this issue. He is encouraging us to set dissolution specifications so that we avoid a situation where the firm has to go to S2 testing frequently.

Barbara

From: Tran, Nhan L
To: Gunther, Sheryl
Cc: Nerurkar, Shriniwas G; Davit, Barbara M
Subject: RE: ANDA 76-387 Clotrimazole Troches, 10 mg (Roxane)

I think that we all agreed with the method, however we have a minor difference on the specification. Your data indicated that the spec of NLT —%/30 min is tight for S1 stage (range ——— %). However, the spec proposed by the firm is wide, i.e., NLT —%/60 minutes (range ——— %).
It is OK with the spec of NLT —%/30 min, but we do not want to set the spec too wide to defeat the purpose of the dissolution testing. How can we distinguish the bad tablet from the good one?
In general (and most of the time) the USP and FDA prefer the Q of NLT —% instead of— % because we want to know when at least — % of the labeled content of the drug is dissolved. Hence, for your ANDA, the Q of NLT —% in 45 minutes seems to be a good balance between our recommendation and the firm's proposal and it is not too wide to be indiscriminating.
Therefore based on the data submitted, I would suggest that the dissolution method and spec for Clotrimazole Troches, ANDA 76-387 are as follows:

Apparatus:	USP 2 (Paddles)
Media:	0.1 N HCl
Volume:	500 mL
Rotational speed:	50 rpm
Temperature:	37.0° ± 0.5° C
Specification:	NLT (Q) — % in 45 minutes.

Please remember that this is my suggestion only. Please discuss it with your TL and the management for their concurrence and decision.
Thanks, for asking as always,

-----Original Message-----
From: Gunther, Sheryl
Sent: Thursday, April 15, 2004 4:24 PM
To: Tran, Nhan L
Subject: ANDA 76-387 Clotrimazole Troches, 10 mg (Roxane)

Tran,

I am reviewing an amendment (ANDA 76-387) submitted by Roxane for the development of a dissolution method for Clotrimazole Troches, 10 mg. Based on our conversation last week, could you please confirm that the method development is acceptable. Barbara is providing confirmation of our proposed dissolution specifications, but asked me to obtain confirmation from you regarding your agreement with their proposed method:

(1) As we discussed, the firm submitted a pH-solubility profile in media with a range of pH of 1.0-8.0. The firm concluded that clotrimazole is only soluble in low pH media, e.g. 0.1 N HCl.

(2) An experimental design was carried out testing parameters for rotational speed and volume. The firm concluded that the conditions of 50 RPM and 500 mL of 0.1 N HCl produced reasonable release rates with minimal agitation and with a volume of media approximating sink conditions.

(3) The firm concluded the optimal test method conditions were the following:

Apparatus:	USP 2 (Paddles)
Media:	0.1 N HCl
Volume:	500 mL
Rotational speed:	50 rpm
Temperature:	37.0° ± 0.5° C

Please let me know if I can provide any further clarification. Also, I have the dissolution data if you would like to see it again.

Thanks so much,

Sheryl

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

CC: ANDA # 76-387
ANDA DUPLICATE
DIVISION FILE
HFD-651/ BIO Drug File
HFD-652/ Reviewer S.D. Gunther
HFD-617/ Project manager A.W. Sigler
HFD-652/ Team Leader S.G. Nerurkar

V:\firmsnz\roxane\ltrs&rev\76387A0304.doc

Endorsements: (Final with Dates)
HFD-652/ S.D. Gunther S.D. Gunther 04/23/2004
HFD-652/ S.G. Nerurkar
HFD-650/ D.P. Conner for BMD 4/23/04

4/23/04

BIOEQUIVALENCE - INCOMPLETE

Submission Date: March 11, 2004

1. **STUDY AMENDMENT (STA)**

Strength: 10 mg
Outcome: IC

Outcome Decisions: **IC - Incomplete**

MAY 3 2004

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-387 Amendment SPONSOR : Roxane Laboratories

DRUG AND DOSAGE FORM : Clotrimazole Troche, 10 mg

STRENGTH(S) : 10 mg

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable pending acceptable response to deficiency comment regarding the dissolution method.

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status: completed on 8/14/03	Inspection results: acceptable
First Generic ____ New facility ____ For cause ____ other ____	Inspection requested: (date) Inspection completed: (date)	

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

INITIAL : Carol Y. Kim DATE : 3/24/04

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

INITIAL : Dena R. Hixon MD DATE : 3/24/04

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

INITIAL : DPC DATE : 5/3/04

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-387
Drug Product Name	Clotrimazole Troche
Strengths	10 mg
Applicant Name	Roxane Laboratories, Inc.
Address	1809 Wilson Road, Columbus, OH 43228
Submission Date(s)	May 4, 2004 (original submission March 28, 2002; acceptable for filing March 29, 2002)
Amendment Date(s)	March 11, 2004, April 2, 2004 (telephone amendment)
Reviewer	Sheryl D. Gunther
First Generic	Potential First Generic
File Location	V:\firmsnz\roxane\ltrs&rev\76387A0504.doc

REVIEW OF AN AMENDMENT

Executive Summary

The firm has submitted its response to the comment made by the Division of Bioequivalence (DBE) in its letter of April 27, 2004. In this amendment, the firm has acknowledged the acceptance of the DBE's recommended dissolution testing specifications. The response is acceptable. The application is now acceptable with no deficiencies.

Background

This drug product requires a BE study with clinical end points. On 3/28/2002, Roxane submitted a BE study with clinical end points. Carol Kim and Dena Hixon found the study deficient (see V:\firmsnz\roxane\ltrs&rev\76387A.mor0302.doc). The firm responded to the deficiencies 2/17/2004, and the clinical endpoint study was found to be acceptable pending a response to the deficiency comment regarding the dissolution method (see V:\firmsnz\roxane\ltrs&rev\76387AM.0204.mor.doc).

Since there is no USP or FDA dissolution testing method for this drug product, the DBE sent a deficiency letter on 2/12/2004 to the firm advising it to develop a dissolution testing method. In the amendment dated March 11, 2004, the firm submitted a response to the bioequivalence deficiency letter which included the development of a dissolution method and dissolution data. However, the firm did not provide comparative dissolution data. Pursuant to a telephone amendment (April 2, 2004), the firm provided comparative dissolution data for 12 units of their product and the reference-listed drug (RLD), Bayer Pharmaceuticals Corporation Mycelex® (clotrimazole) troches, 10 mg, obtained under the testing conditions deemed optimal (Apparatus II @ 50 rpm, 500 mL of 0.1N HCl). The dissolution method and comparative dissolution data was found to be acceptable; however, the Division of Bioequivalence (DBE) did not agree with the firm's proposed dissolution specification (NLT— % (Q) in 60 minutes) and recommended

the dissolution specification be revised (NLT —% (Q) in 45 minutes). The application was incomplete pending the firm's acceptance of the DBE's recommended dissolution specifications.

DBE Comment I

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.

Firm's Response

The firm has accepted the above dissolution specification recommended by the DBE.

The firm's reply to the comment is acceptable.

Recommendation

The firm has committed to adopt the dissolution method and specifications recommended by the Division of Bioequivalence.

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.

No further action is needed.

Sheryl D. Gunther 5/13/2004

Sheryl D. Gunther, Pharm.D., Reviewer, Branch I Date

5/13/2004

Shriniwas G. Nerurkar, Ph.D., Team Leader, Branch I Date

CC: ANDA # 76-387
ANDA DUPLICATE
DIVISION FILE
HFD-651/ BIO Drug File
HFD-652/ Reviewer S.D. Gunther
HFD-617/ Project manager A.W. Sigler
HFD-652/ Team Leader S.G. Nerurkar

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Endorsements: (Final with Dates)
HFD-652/ S.D. Gunther S. D. Gunther 5/13/2004
HFD-652/ S.G. Nerurkar 5/13/04
HFD-650/ D.P. Conner 5/14/04

BIOEQUIVALENCE - ACCEPTABLE

Submission Date: May 4, 2004

1. **STUDY AMENDMENT (STA)**

Strength: 10 mg
Outcome: WC

Outcome Decisions: **AC - Acceptable**

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

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HFD-650/ D.P. Conner BMO 5/14/04

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Submission Date: May 4, 2004

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Strength: 10 mg
Outcome: WC

Outcome Decisions: **AC - Acceptable**

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OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-387/Amendment **SPONSOR:** Roxane Laboratories, Inc.

DRUG AND DOSAGE FORM: Clotrimazole Troche

STRENGTH(S): 10 mg

TYPES OF STUDIES: N/A

CLINICAL STUDY SITE(S): N/A

ANALYTICAL SITE(S): N/A

STUDY SUMMARY: The application is acceptable.

DISSOLUTION: N/A

DSI INSPECTION STATUS

Inspection needed: N.A.		Inspection status:	Inspection results:
First Generic	Potential first generic	Inspection requested: (date)	
New facility		Inspection completed: (date)	
For cause			
Other			

PRIMARY REVIEWER : Sheryl D. Gunther, Pharm.D. **BRANCH :** I

INITIAL : SDG **DATE :** 5/13/2004

TEAM LEADER : Shriniwas Nerurkar, Ph.D. **BRANCH :** I

INITIAL : [signature] **DATE :** 5/13/2004

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

INITIAL : BM C **DATE :** 5/14/04

JR