CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-419

Generic Name: Ketoconazole Shampoo, 2%

Sponsor: Clay-Park Labs, Inc.

Approval Date: January 7, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-419

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Statistical Review(s)	X
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-419

APPROVAL LETTER

ANDA 76-419

JAN 7 2004

Clay-Park Labs, Inc.
Attention: Candis Edwards
1700 Bathgate Avenue
Bronx, NY 10457

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated May 24, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ketoconazole Shampoo, 2%.

Reference is also made to your amendments dated December 31, 2002, and January 6, March 6, May 6, December 4, December 23, December 29, and December 30, 2003.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ketoconazole Shampoo, 2%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Nizoral® Shampoo, 2%, of McNeil Consumer and Specialty Pharmaceuticals.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy, which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 1/7/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-419

FINAL PRINTED LABELING

76-419

APPROVED

NDC 45802-465-64

KETOCONAZOLE
SHAMPOO, 2%

For topical application only.

4 fl oz

Rx only

JAN 07 2004

Mfg. by:
Clay-Park Labs, Inc.
Bronx, NY 10457

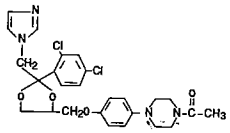
LCPL46564-4X N0402

Ketoconazole Shampoo, 2%
Rx only

DESCRIPTION

Ketoconazole Shampoo, 2% is a red-orange liquid for topical application, containing the broad-spectrum synthetic antifungal agent ketoconazole in a concentration of 2% in an aqueous suspension. It also contains: coconut fatty acid diethanolamide, disodium laureth sulfosuccinate, FD & C Red No. 40, hydrochloric acid, imidurea, laurdimonium hydroxypropyl hydrolyzed collagen, PEG-120 methyl glucose dioleate, sodium chloride, sodium hydroxide, sodium lauryl ether sulfate, and purified water.

Ketoconazole is cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine and has the following structural formula:



CLINICAL PHARMACOLOGY

Tinea (pityriasis) versicolor is a non-contagious infection of the skin caused by *Pityrosporum orbiculare (Malassezia furfur)*. This commensal organism is part of the normal skin flora. In susceptible individuals the condition is often recurrent and may give rise to hyperpigmented or hypopigmented patches on the trunk which may extend to the neck, arms and upper thighs. Treatment of the infection may not immediately result in restoration of pigment to the affected sites.

Normalization of pigment following successful therapy is variable and may take months, depending on individual skin type and incidental skin exposure. The rate of recurrence of infection is variable.

When ketoconazole shampoo, 2% was applied dermally to intact or abraded skin of rabbits for 28 days at doses up to 50 mg/kg and allowed to remain one hour before being washed away, there were no detectable plasma ketoconazole levels using an assay method having a lower detection limit of 5 ng/mL. Ketoconazole was not detected in plasma in 39 patients who shampooed 4-10 times per week for 6 months or in 33 patients who shampooed 2-3 times per week for 3-26 months (mean: 16 months).

An exaggerated use washing test on the sensitive antecubital skin of 10 subjects twice daily for five consecutive days showed that the irritancy potential of ketoconazole shampoo, 2% was significantly less than that of 2.5% selenium sulfide shampoo.

A human sensitization test, a phototoxicity study, and a photoallergy study conducted in 38 male and 22 female volunteers showed no contact sensitization of the delayed hypersensitivity type, no phototoxicity and no photoallergenic potential due to Ketoconazole Shampoo, 2%.

Mode of Action: Interpretations of *in vivo* studies suggest that ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes.

It is postulated, but not proven, that the therapeutic effect of ketoconazole in tinea (pityriasis) versicolor is due to the reduction of *Pityrosporum orbiculare (Malassezia furfur)* and that the therapeutic effect in dandruff is due to the reduction of *Pityrosporum ovale*. Support for the therapeutic effect in tinea versicolor comes from a three-arm, parallel, double-blind, placebo-controlled study in patients who had moderately severe tinea (pityriasis) versicolor. Successful response rates in the primary efficacy population for each of both three-day and single-day regimens of ketoconazole shampoo, 2% were statistically significantly greater (73% and 69%, respectively) than a placebo regimen (5%). There had been mycological confirmation of fungal disease in all cases at baseline. Mycological clearing rates were 84% and 78%, respectively, for the three-day and one-day regimens of the 2% shampoo and 11% in the placebo regimen. While the differences in the rates of successful response between either of the two active treatments and placebo were statistically significant, the difference between the two active regimens was not.

Microbiology: Ketoconazole is a broad-spectrum synthetic antifungal agent which inhibits the growth of the following common dermatophytes and yeasts by altering the permeability of the cell membrane: dermatophytes: *Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis, M. audouini, M. gypseum* and *Epidermophyton floccosum*: yeasts; *Candida albicans, C. tropicalis, Pityrosporum ovale (Malassezia ovale)* and *Pityrosporum orbiculare (M. furfur)*. Development of resistance by these microorganisms to ketoconazole has not been reported.

INDICATIONS AND USAGE
Ketoconazole Shampoo, 2% is indicated for the treatment of tinea (pityriasis) versicolor caused by or presumed to be caused by *Pityrosporum orbiculare* (also known as *Malassezia furfur or M. orbiculare).*

Note: Tinea (pityriasis) versicolor may give rise to hyperpigmented or hypopigmented patches on the trunk which may extend to the neck, arms and upper thighs. Treatment of the infection may not immediately result in normalization of pigment to the affected sites. Normalization of pigment following successful therapy is variable and may take months, depending on individual skin type and incidental sun exposure. Although tinea versicolor is not contagious, it may recur because the organism that causes the disease is part of the normal skin flora.

CONTRAINDICATIONS
Ketoconazole Shampoo, 2% is contraindicated in persons who have shown hypersensitivity to the active ingredient or excipients of this formulation.

PRECAUTIONS
General: If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.

Information for Patients: May be irritating to mucous membranes of the eyes and contact with this area should be avoided.

There have been reports that use of the shampoo resulted in removal of the curl from permanently waved hair.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames Salmonella microsomal activator assay was also negative. A long-term feeding study of ketoconazole in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity, when fed at doses up to 80 mg/kg/day.

Pregnancy: Teratogenic effects: Pregnancy Category C: Ketoconazole is not detected in plasma after chronic shampooing. Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given orally in the diet at 80 mg/kg/day (10 times the maximum recommended human oral dose). However, these effects may be related to maternal toxicity, which was seen at this and higher dose levels.

There are no adequate and well-controlled studies in pregnant women. Ketoconazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: Ketoconazole is not detected in plasma after chronic shampooing. Nevertheless, caution should be exercised when Ketoconazole Shampoo, 2% is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
In 11 double-blind trials in 264 patients using Ketoconazole Shampoo, 2% for the treatment of dandruff or seborrheic dermatitis, an increase in normal hair loss and irritation occurred in less than 1% of patients. In three open-label safety trials in which 41 patients shampooed 4-10 times weekly for six months, the following adverse experiences each occurred once: abnormal hair texture, scalp pustules, mild dryness of the skin, and itching. As with other shampoos, oiliness and dryness of hair and scalp have been reported. In a double-blind, placebo-controlled trial in which patients with tinea versicolor were treated with either a single application of Ketoconazole Shampoo, 2% (n=106), a daily application for three consecutive days (n=107), or placebo (n=105), drug-related adverse events occurred in 5 (5%), 7 (7%) and 4 (4%) of patients, respectively. The only events that occurred in more than one patient in any one of the three treatment groups were pruritus, application site reaction, and dry skin; none of these events occurred in more than 3% of the patients in any one of the three groups.

OVERDOSAGE
Ketoconazole Shampoo, 2% is intended for external use only. In the event of accidental ingestion, supportive measures should be employed. Induced emesis and gastric lavage should usually be avoided.

DOSAGE AND ADMINISTRATION
Apply the shampoo to the damp skin of the affected area and a wide margin surrounding this area. Lather, leave in place for 5 minutes, and then rinse off with water.

One application of the shampoo should be sufficient.

HOW SUPPLIED
Ketoconazole Shampoo, 2% is a red-orange liquid supplied in a 4-fluid ounce nonbreakable plastic bottle.

Storage conditions: Store at a temperature not above 25°C (77°F). Protect from light.

Mfg. by: **Clay-Park Labs, Inc.**
Bronx, NY 10457

APPROVED

JAN 07 2004

NDC 45802-465-64

KETOCONAZOLE
SHAMPOO, 2%

For topical application only.

4 fl oz

Rx only

Mfg. by:
Clay-Park Labs, Inc.
Bronx, NY 10457

KETOCONAZOLE
SHAMPOO, 2%

APPROVED

Dosage:
One application of the shampoo should be sufficient and then intermittently as needed.

Directions for Use
Apply the shampoo to the damp skin of the affected area and a wide margin surrounding this area. Lather, leave in place for 5 minutes, and then rinse off with water.

Active ingredient: ketoconazole
Inactive ingredients: coconut fatty acid diethanolamide, disodium laureth [illegible] FD&C Red No. 40, [illegible] acid, hydroxypropyl methyl cellulose, PEG-120 methyl glucose dioleate, sodium chloride, sodium hydroxide, sodium lauryl ether sulfate, and purified water.

Store at a temperature not above 25°C (77°F). Protect from light.

Mfg. by: **Clay-Park Labs, Inc.**
Bronx, NY 10457 R46564CPL-4X RD402

0 81642 46564 8

(BACK LABEL)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-419

CSO LABELING REVIEW(S)

****First Generic****
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-419
Date of Submission: January 6, 2003
Applicant's Name: Clay-Park Labs, Inc.
Established Name: Ketoconazole Shampoo, 2%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER – 4 ounce bottle (120 mL)
Satisfactory in final print as of the January 6, 2003 submission. (Vol A2.1)

INSERT:
Satisfactory in final print as of the January 6, 2003 submission; Rev.0402 (Vol A2.1)

Revisions needed post-tentative approval: YES. The following are requested labeling revisions from my review of your amendment dated January 6, 2003 for ANDA 76-419 for Ketoconazole Shampoo, 2%. The revisions are **"POST-APPROVAL"** revisions and may be submitted in an annual report provided the changes are described in full.

INSERT

DESCRIPTION-Revise the chemical name to read: " (±)- cis-1-Acetyl-4-[p-[[2-(2,4-dichlorophenyl)-2-(imidazol-1- ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine"

CLINICAL PHARMACOLOGY, Microbiology subsection, first sentence- Revise to read: "*...floccosum;* yeast: *Candida...Pityrosporum ovale* and *Pityrosporum...*"

PRECAUTIONS, Carcinogenesis, Mutagenesis, Impariment of Fertility subsection, last sentence- Revise to read: "A long-term study of..."

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Nizoral 2% Shampoo
NDA Number: 19-927
NDA Drug Name: Nizoral Shampoo, 2%
NDA Firm: McNeil Consumer Healthcare
Date of Approval of NDA Insert & supplement: NDA 19-927/S-014; revised October 2, 1997; Approved October 10, 1997
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

PATENTS/EXCLUSIVITIES: ANDA applicant filed PIII

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019927	001	4942162	FEB 11,2003	

Exclusivity Data

There is no unexpired exclusivity for this product.

REVIEW OF PROFESSIONAL LABELING CHECK LIST
(Comments from previous reviewer)

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD: (* FIRST GENERIC *****)**

1. MODEL LABELING-The review was based on the labeling for the reference listed drug (Nizoral Shampoo, 2%; NDA 19-927/S-014 – McNeil Consumer Healthcare; revised October 2, 1997; approved in draft October 10, 1997)

(Comments from previous reviewer)

2. Packaging
   The RLD packages its product in 4 ounce bottles

   The applicant is proposing to package its' product in 4 ounce bottles.

3. Inactive Ingredients – There does not appear to be a discrepancy between the listing in inactives in the DESCRIPTION section of the insert labeling and the C&C Statements. (see pg 2863 in vol. B. 1.1)

4. RLD - Store at a temperature not above 25°C(77°C). Protect from light.
   ANDA – Same as RLD

5. Patent Data: Paragraph III filed by firm

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019927	001	4942162	FEB 11,2003	

Exclusivity Data

There is no unexpired exclusivity for this product.

Date of Review: January 13, 2003 Date of Submission: January 6, 2003

Primary Reviewer: Ruby Wu RWu Date: 1/15/03

Team Leader: John Grace John J Grace Date: 1/15/2003

cc: ANDA: 76-419
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSAM\CLAYPARK\LTRS&REV\76419.ap.L.doc
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-419
Date of Submission: May 24, 2002
Applicant's Name: Clay-Park Labs, Inc.
Established Name: Ketoconazole Shampoo, 2%

Labeling Deficiencies:

1. **CONTAINER** – 4 ounce bottle (120 mL)
   Back Panel: Note that "KETOCONAZOLE" was spelled incorrectly.

2. **INSERT** –
   a. PRECAUTIONS
      Carcinogenesis, Mutagenesis, Impairment of Fertility: Last sentence; revise to read as follows -

      ...no evidence of oncogenic activity, when fed at doses up to 80 mg/kg/day.

   b. HOW SUPPLIED
      We encourage you to include the "Manufactured by" statement at the end of this section.

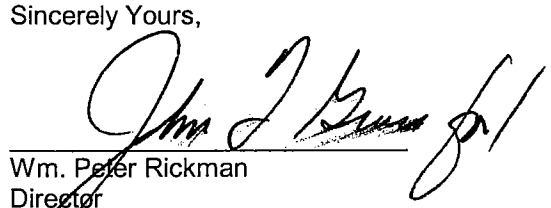
Please revise your labels and labeling, then prepare and submit 12 copies of final print.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

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

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

Sincerely Yours,



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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			

Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD: (* FIRST GENERIC *****)**

1. Labeling review was NOT based on the labeling for the reference listed drug (Nizoral Shampoo, 2%; NDA 19-927/S-014 – Janssen Research Foundation; approved in draft October 10, 1997.)

2. Packaging
   The RLD packages its product in 4 ounce bottles

   The applicant is proposing to package its' product in 4 ounce bottles.

3. Inactive Ingredients – There does not appear to be a discrepancy between the listing in inactives in the DESCRIPTION section of the insert labeling and the C&C Statements. (see pg 2863 in vol. B. 1.1)

4. RLD - Store at a temperature not above 25°C(77°C). Protect from light.
   ANDA – Same as RLD

Date of Review:
November 30, 2002

Date of Submission:
May 24, 2002

Primary Reviewer:
J Barlow

Date: 12/2/02

Team Leader:
J Grace

Date: 12/2/02

cc: ANDA 76-419
DUP/DIVISION FILE
HFD-613/JBarlowforRWu/JGrace (no cc)
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Review

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-419

CHEMISTRY REVIEW(S)

ANDA 76-419

Ketoconazole Shampoo, 2%

Clay-Park Labs, Inc.

Benjamin Lim
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-419

2. REVIEW #1

3. REVIEW DATE: 9/26/2002

4. REVIEWER: Benjamin Lim

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Clay-Park Original Submission	5/24/2002
Information Amendment	7/11/2002
FDA Acknowledgement Letter	7/15/2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original ANDA	5/24/2002

7. NAME & ADDRESS OF APPLICANT:

Name: Clay-Park Labs, Inc.

Address: 1700 Bathgate Avenue

Bronx, NY 10457

Representative: Candis Edwards

Telephone: (718)960-9976

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ketoconazole Shampoo, 2%

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Clay-Park Labs, Inc.'s proposed ANDA for Ketoconazole Shampoo, 2% is the approved, reference listed drug, NIZORAL® (ketoconazole) 2% Shampoo, the subject of NDA #019927, held by McNeil Consumer Healthcare, containing 2% ketoconazole. Clay-Park has submitted the revised FDA Form 356h, based on teleconference with Paras Patel (FDA), to correct the holder of NDA #019927 from Janssen Pharmaceutical Inc., to McNeil Consumer Healthcare (Received June 12, 2002; V. 2.1 Attachment 1).

b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, current through December 2001, there is no unexpired marketing exclusivity for NIZORAL® (ketoconazole) 2% Shampoo, under section 505(j)(4)(D) of the Act.

c. US Patent # 4,942,162 which claims the use of the listed drug to treat seborrheic dermatitis, will expire on February 11, 2003. Should this ANDA be approved prior to the expiration date of the patent, Clay-Park Labs, Inc. will not market Ketoconazole Shampoo, 2%, until after the expiration of US Patent # 4,942,162.

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Shampoo

12. STRENGTH/POTENCY: 2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx

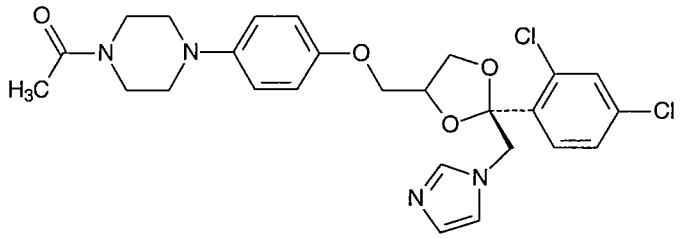
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ketoconazole. Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, *cis*-.$C_{26}H_{28}Cl_2N_4O_4$. 531.44. 65277-42-1. Antifungal.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]				3	Adequate	5/13/2002	May 21, 2002 document is not an amendment.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

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18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	7/22/02	D'Ambrogio, J.
Methods Validation	Pending		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-419

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Clay-Park's proposed drug product, Ketoconazole Shampoo, 2%, is based on the listed drug, NIZORAL® (ketoconazole) 2% Shampoo of McNeil Consumer Healthcare (NDA # 019927). Clay-Park's drug product is a orange to red, viscous liquid. Clay-Park uses [redacted] (Imidurea) as a [redacted] in their formulation. Clay-Park's Ketoconazole Shampoo, 2% is packaged in 4 oz HDPE, tapered, oval bottle with a White [redacted] dispensing closure.

Ketoconazole, USP drug substance is a white or almost white crystalline powder. The [redacted] used by Clay-Park is [redacted] and the DMF # [redacted] referenced for [redacted] was found adequate on 05/13/2002.

Ketoconazole Shampoo, 2% is not an USP compendial item, therefore, analytical method validation package for the drug product was submitted to the District Laboratory for validation purposes.

B. Description of How the Drug Product is Intended to be Used

Topical administration for treatment of tinea (pityriasis) versicolor.

C. Basis for Approvability or Not-Approval Recommendation

There are CMC deficiencies

III. Administrative

A. Reviewer's Signature

11/13/02

B. Endorsement Block

HFD-620/ Benjamin Lim, Ph.D./10-17-02 11/13/02
HFD-620-/Shing Liu, Ph.D./10-18-02 S. H. Liu 11/13/02
HFD-617/Wanda Panphile, PM/10-25-02

C. CC Block

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ON ORIGINAL

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Page(s) of trade secret and /or confidential commercial information

ANDA 76-419

Ketoconazole Shampoo, 2%

Clay-Park Labs, Inc.

Benjamin Lim, Ph.D.
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-419

2. REVIEW #2

3. REVIEW DATE: 11/25/2003

4. REVIEWER: Benjamin Lim

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Clay-Park Original Submission	5/24/2002
Information Amendment	7/11/2002
FDA Acknowledgement Letter	7/15/2002
T-con	12/3/2002
Labeling Amendment	1/6/2003
Chemistry NA Letter	11/15/2002
Chemistry Amendment	12/31/2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Chemistry Amendment	12/31/2002
Labeling NA Letter	12/9/2002
Telephone Amendment (CMC)	3/6/2003
Bio Deficiency Letter	5/1/2003
Telephone Amendment (Bio)	5/6/2003
Patent Amendment (new patent certification)	12/4/03
Telephone Amendment	12/23/03
Telephone Amendment	12/29/03
Telephone Amendment	12/30/03

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Clay-Park Labs, Inc.
Address:	1700 Bathgate Avenue
	Bronx, NY 10457
Representative:	Candis Edwards
Telephone:	(718) 960-9976

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ketoconazole Shampoo, 2%

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Clay-Park Labs, Inc.'s proposed ANDA for Ketoconazole Shampoo, 2% is the approved, reference listed drug, NIZORAL® (ketoconazole) 2% Shampoo, the subject of NDA #019927, held by McNeil Consumer Healthcare, containing 2% ketoconazole. Clay-Park has submitted the revised FDA Form 356h, based on teleconference with Paras Patel (FDA), to correct the holder of NDA #019927 from Janssen Pharmaceutical Inc., to McNeil Consumer Healthcare (Received June 12, 2002; V. 2.1 Attachment 1).

b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, current through December 2001, there is no unexpired marketing exclusivity for NIZORAL® (ketoconazole) 2% Shampoo, under section 505(j)(4)(D) of the Act.

c. US Patent # 4,942,162, which claims the use of the listed drug to treat seborrheic dermatitis, expired February 11, 2003. Clay-Park Labs, Inc. acknowledged the expiration of US Patent # 4,942,162 by submitting a paragraph II certification 12/4/03 .

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Shampoo

12. STRENGTH/POTENCY: 2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx

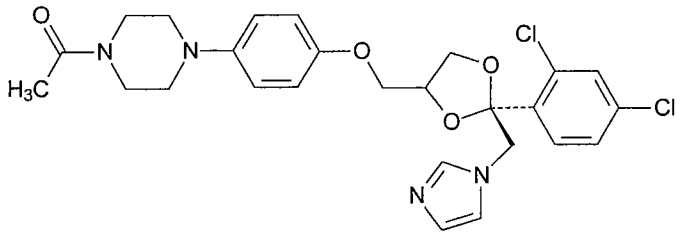
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ketoconazole. Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, *cis*-.$C_{26}H_{28}Cl_2N_4O_4$. 531.44. 65277-42-1.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]				3	Adequate	5/13/2002	May 21, 2002 document is not an amendment.
				4			
				4			

[1] Action codes for DMF Table:
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Other codes indicate why the DMF was not reviewed, as follows:
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5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	See Review #1		
EES	Acceptable	7/22/02	D'Ambrogio, J.
Methods Validation	Acceptable	4/9/03	
Labeling	Acceptable	1/15/03	R.Wu
Bioequivalence	Acceptable	11/4/03	Carol Kim
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: Minor Amendment

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-419

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Clay-Park's proposed drug product, Ketoconazole Shampoo, 2%, is based on the listed drug, NIZORAL® (ketoconazole) 2% Shampoo of McNeil Consumer Healthcare (NDA # 019927). Clay-Park's drug product is a orange to red, viscous liquid. Clay-Park uses [redacted] (Imidurea) as a [redacted], in their formulation. Clay-Park's Ketoconazole Shampoo, 2% is packaged in 4 oz HDPE, tapered, oval bottle with a White [redacted], dispensing closure.

Ketoconazole, USP drug substance is a white or almost white crystalline powder. The [redacted] used by Clay-Park is [redacted] and the DMF #[redacted], referenced for [redacted], was found adequate on 05/13/2002.

Ketoconazole Shampoo, 2% is not an USP compendial item, therefore, analytical method validation package for the drug product was submitted to the District Laboratory for validation purposes.

B. Description of How the Drug Product is Intended to be Used

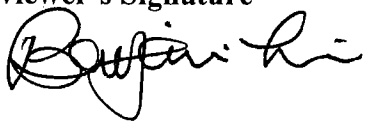
Topical administration for treatment of tinea (pityriasis) versicolor.

C. Basis for Approvability or Not-Approval Recommendation

The CMC, bioequivalence and labeling sections are acceptable. The MV package and EER was also found acceptable. The ANDA is approvable.

III. Administrative

A. Reviewer's Signature



B. Endorsement Block

HFD-620/ Benjamin Lim, Ph.D./ 1/05/04
HFD-620-/Shing Liu, Ph.D./ S.H.Liu 1/5/04
HFD-617/Wanda Pamphile, Pharm.D./ 1/5/04

C. CC Block

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Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-419

Statistical Review

ANDA 76-419
Drug Product : Ketoconazole Shampoo, 2%
Sponsor: Clay-Park Lab., Inc.
Reference Listed Drug (RLD): Nizoral® Shampoo 2%
McNeil Consumer, Inc.
Submission Date: May 24, 2002

Reviewer: Huaixiang Li, Ph.D., QMRS/OB/CDER
Requestor: Dena Hixon, MD, Carol Kim, Pharm.D., OGD/CDER, 7/14/03
V:\frimsnz\claypark\ltr&rev\76419st.doc

Remarks

The sponsor submitted one CD-ROM containing data on all variables collected in the Case Report Form (CRF) per patient on May 24, 2002. Another data set included data from an additional fifty patients in the Evaluable population (EP)*, following the FDA medical reviewer's recommendation (May 6, 2003).

The statistical analyses used information from both sources.

The following adjustments to these submitted data sets were made in accordance with recommendations of OGD medical reviewers.

1) Three patients - #7, 576 and 580 - were included in the EP population, as recommended by the medical reviewer. These three patients had not been included in the EP in the additional data set.

2) Patient #25 was excluded from the EP at visit 3 due to missing this visit. Patient #345 was excluded from the EP at visit 4 due to falling outside of the visit window (day 39).

3) Patients #35 and 405 were excluded from the EP and patients #514 and 52 were included in the EP at visit 4*.

*: Please see the details in the FDA medical reviewer's report.

Objectives of the study

The primary objective of the study was to establish the bioequivalence of the test product, Clay-Park Lab., Inc., Ketoconazole Shampoo, 2%, and the reference product, McNeil Consumer, Inc., Nizoral® Shampoo 2%, and to show superiority of the two active treatments to the placebo, a shampoo vehicle, in the treatment of tinea versicolor following a single application.

Study Design

This was a 3 arm parallel double-blind study for patients with signs and symptoms of tinea versicolor. The three shampoos were the test product, Clay-Park Lab., Inc., Ketoconazole Shampoo, 2%, the reference product, McNeil Consumer, Inc., Nizoral® Shampoo 2%, and the placebo, a shampoo vehicle.

A total of 501 patients were enrolled and randomly assigned to three treatment groups in the study. At the enrollment visit, the total signs/symptoms score was calculated as the sum of the scores of four elements, erythema, pruritus, scaling/desquamation, and hyper-/hypopigmentation, each scored as (0=absent, 1=mild, 2=moderate, 3=severe). Either a cellophone tape test or KOH preparation was performed to confirm fungal diagnosis of tinea versicolor.

The eligible patients, who had at least one of the primary signs/symptoms present ($\geq$2) and total overall scores $\geq$ 4, and positive fungal diagnosis, were instructed to apply the shampoo to all affected areas of the body for 5 minutes on the day/evening of visit 1. The signs/symptoms scoring and fungal evaluation were performed at visit 2 (Day 2-5, safety evaluation), visit 3 (Day 8-10, safety evaluation), and visit 4 (Day 31, with window –5 /+7 days, primary endpoint evaluation). The physician's global assessment (PGA) was graded at visits 3 and 4 as (1=healed, 2=markedly improved, 3=considerable reduction, 4=no change, 5=worsening).

Outcome Variables

The sponsor and FDA medical officer defined the primary endpoint to be therapeutic success rate at visit 4 (Day 31). The secondary endpoint was the therapeutic success rate at visit 3 (Day 8).

Therapeutic success at visits 3 and 4 was defined as satisfying all of the following:

1) a PGA Evaluation of "healed" (=1);
2) severity scores on the individual signs/symptoms:
   - erythema (=0)
   - pruritus (=0)
   - scaling/desquamation (=0)
   - hyper/hypopigmentation ($\leq$ 2)
3) absence of fungal hyphae.

Statistical Analysis Methods

Efficacy Analysis

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

The efficacy analyses for the therapeutic success rate were carried out by using Fisher's exact test (one-sided) for each active treatment versus placebo with a 1-sided significance level of α=0.025.

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

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -.20$
or $p_T - p_R > .20$

versus

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

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

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

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

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

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

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

We reject H_0 if $L \geq -.20$ and $U \leq .20$

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

Analysis Populations

Two analysis populations were defined in the FDA medical reviewer's report:

Intent-to-treat population (ITT) – All subjects randomized to treatment and treated, with at least one post-baseline visit.
Evaluable population (EP) – All subjects in the ITT population who completed the study and were evaluable for the analyses based on the protocol and FDA medical reviewer's best judgement.

According to the FDA medical reviewers, the determination of clinical equivalence of the two active treatments was to be assessed using the evaluable population (EP), while the superiority comparison of the two active treatments to placebo was to be assessed using the intent-to-treat population (ITT).

Statistical Analysis Results

A total of 501 patients were enrolled. The ITT population included 495 patients. The EP included 469 patients at visit 3 and 453 patients at visit 4.

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

	Clay-Park	McNeil	Placebo	Total
Safety	202	198	101	501
Intent-to-treat (ITT)	**199**	**196**	**100**	**495**
Evaluable (EP) at visit 3 (Day 8)	187	187	95	469
Evaluable (EP) at visit 4 (Day 31)	**182**	**180**	**91**	**453**

*: Please see details for reasons of exclusion in the FDA medical reviewer's report.

Demographics and baseline

The mean age was 34.6 years and the age ranged from 12.2 to 77.1 years old in the ITT population. The table below shows the sex and race distribution for the ITT population. The age, sex, and race of patients were comparably distributed among the three treatment groups for the ITT and EP populations, based on chi-square tests.

	Clay-Park	McNeil	Placebo	Total
Sex				
Female	86	77	48	211
Male	113	119	52	284
Race				
White	175	163	85	423
Hispanic	12	17	9	38
Black	10	9	6	25
Others	2	7	0	9

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

Efficacy and equivalence Analyses

We analyzed the data for efficacy and equivalence for the therapeutic success rate at visits 3 and 4.

Primary endpoint: Therapeutic success rate at visit 4 (Day 31).

Efficacy and equivalence analyses for primary endpoint

Population	Test* % successes (No. of successes/total number)	Reference* % successes (No. of successes/total number)	Placebo* % successes (No. of successes/total number)	p-value# for Test vs. Placebo	p-value# for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
ITT	60.8 (121/199)	58.7 (115/196)	10.0 (10/100)	<0.001	<0.001		
EP	62.6 (114/182)	61.1 (110/180)	8.8 (8/91)			-7.4, 10.5	Yes

*: The rate of success equals the number of successes divided by the total number, then multiplied by 100.
#: The p-values were from Fisher's exact test (1-sided).

The two active treatments were significantly better than placebo ($p \leq 0.001$) for the ITT population and the equivalence test was passed for the EP population for the therapeutic success rate at visit 4 (Day 31).

Secondary endpoints: Therapeutic success rate at visit 3 (Day 8).

Efficacy and equivalence analyses for secondary endpoints

Population	Test* % successes (No. of successes/total number)	Reference* % successes (No. of successes/total number)	Placebo* % successes (No. of successes/total number)	p-value for Test vs. Placebo	p-value for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
ITT	11.6 (23/199)	7.1 (14/196)	5.0 (5/100)	0.048	0.330		
EP	12.3 (23/187)	5.9 (11/187)	5.3 (5/95)			1.0, 11.8	Yes

The two active treatments were better, but not statistically significantly better (at the 1-sided $\alpha=0.025$ level) than placebo ($p=0.048$ for Test, $p=0.330$ for Ref.) for the ITT population for the therapeutic success rate at visit 3. The equivalence test was passed for the EP population for the therapeutic success rate at visit 3 (Day 8).

Safety

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

Conclusion

Efficacy:

Primary endpoint: The two active treatments were significantly better than placebo ($p \leq 0.001$) for the ITT population and the equivalence test was passed for the EP populations for the therapeutic success rates at visit 4 (Day 31).

Secondary endpoint: The two active treatments were better, but not statistically significantly better (at the 1-sided α=0.025 level) than placebo (p=0.048 for Test, p=0.330 for Ref.) for the ITT population for the therapeutic success rate at visit 3. The equivalence test was passed for the EP population for the therapeutic success rate at visit 3 (Day 8).

Huaixiang Li 10/22/03

Huaixiang Li, Ph.D.
Mathematical Statistician, QMR

Donald J. Schuirmann 10/20/03

Donald J. Schuirmann
Expert Mathematical Statistician, QMR

Stella G. Machado 10/20/03

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

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

APPEARS THIS WAY
ON ORIGINAL

Clay-Park Labs, Inc./Agis Group
1700 Bathgate Avenue
Bronx, New York 10457
United States

Ketoconazole Shampoo, 2%
Protocol CPL-102

A Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Bioequivalence of Clay-Park Labs, Inc.'s Ketoconazole Shampoo, 2% and Nizoral® (Ketoconazole) 2% Shampoo in Subjects with Tinea Versicolor

Design Synopsis: This double-blind, randomized, parallel-group, placebo-controlled, multi-center study included a Screening visit (Visit 1, Day 1), a Safety visit (Visit 2, Day 2-5), and two After Treatment Follow-up visits (Visit 3, Day 8-10, and Visit 4, Day 29-33).

Investigators: 25 Investigators in the United States (see pages iii and iv for list).

Study Period: First Subject Visit July 25, 2001
Last Subject Visit February 27, 2002

Study Phase: III

Indication Studied: Tinea Versicolor

Sponsor: Clay-Park Labs, Inc./Agis Group
Sponsor Contact: Candis Edwards, M.S. Telephone: 718-960-9976
Director, Regulatory Affairs Facsimile: 718-960-0111

Contract Research Organization (CRO)

Report Date: April 29, 2002

GCP Compliance Statement: This study was performed in compliance with Good Clinical Practices, including archiving of essential documents.

Table 3.1
Enrollment by Investigator

Site Number	Principal Investigator	Number of Subjects: Randomized	Day 8 Per-Protocol Analyses[1]	Day 31 Per-Protocol Analyses[1]	Intent-to-Treat Analyses[2]
1		19	14	12	19
2		20	19	19	20
3		25	17	16	23
5		19	17	15	19
6		25	19	16	25
7		15	12	9	15
8		15	13	12	15
9		25	23	22	24
10		15	13	11	15
11		15	14	13	15
12		15	12	12	15
13		65	64	64	65
14		9	4	2	9
15		20	16	13	20
17		15	6	3	15
19		35	31	28	35
20		10	8	7	9
21		15	11	11	15
22		5	5	4	5

(continued)

APPEARS THIS WAY
ON ORIGINAL

Table 3.1 (Cont.)
Enrollment by Investigator

Site Number	Principal Investigator	Number of Subjects: Randomized	Day 8 Per-Protocol Analyses[1]	Day 31 Per-Protocol Analyses[1]	Intent-to-Treat Analyses[2]
23		24	19	13	24
24		15	14	13	15
25		15	14	12	15
26		20	16	13	20
27		25	20	17	24
28		20	15	13	19
Total		501	416	370	495

[1]Evaluated for efficacy.
[2]Evaluated for safety and efficacy.

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ON ORIGINAL

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Page(s) of trade secret and /or confidential commercial information

Table 3.3
Demographic Characteristics for Intent-to-Treat Subjects by Investigator
(Gender, Race, and Age)

Parameter	Ketoconazole Shampoo, 2% (N=199)	Nizoral® (ketoconazole) 2% Shampoo (N=196)	Vehicle (N=100)
Gender(n,%)			
	4 (50%)	5 (71%)	2 (50%)
	4 (50%)	2 (29%)	2 (50%)
	6 (75%)	8 (100%)	3 (75%)
	2 (25%)	0 (0%)	1 (25%)
	5 (56%)	7 (78%)	0 (0%)
	4 (44%)	2 (22%)	5 (100%)
	6 (75%)	3 (43%)	2 (50%)
	2 (25%)	4 (57%)	2 (50%)
	3 (30%)	9 (90%)	3 (60%)
	7 (70%)	1 (10%)	2 (40%)
	4 (67%)	4 (67%)	3 (100%)
	2 (33%)	2 (33%)	0 (0%)
	3 (50%)	4 (67%)	1 (33%)
	3 (50%)	2 (33%)	2 (67%)
	6 (67%)	4 (40%)	2 (40%)
	3 (33%)	6 (60%)	3 (60%)
	1 (17%)	3 (50%)	3 (100%)
	5 (83%)	3 (50%)	0 (0%)
	4 (67%)	3 (50%)	1 (33%)
	2 (33%)	3 (50%)	2 (67%)

(continued)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-419

BIOEQUIVALENCE REVIEW(S)

NOV 4 2003

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-419 SPONSOR : Clay-Park Labs. Inc.

DRUG AND DOSAGE FORM : Ketoconazole Shampoo, 2%

STRENGTH(S) : 2%

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / ~~NO~~	Inspection status: completed on 7/2/03	Inspection results: acceptable
First Generic _____ New facility _____ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

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

INITIAL : _____ DATE : 10/29/03

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

INITIAL : DRH DATE : 10/29/03

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

INITIAL : _____ DATE : 11/4/03

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-419 APPLICANT:Clay-Park Labs. Inc.

DRUG PRODUCT: Ketoconazole Shampoo, 2%

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

The data submitted to ANDA 76-419, using the primary endpoint of therapeutic success rate at the follow-up visit (day 31, visit 4), are adequate to demonstrate bioequivalence of Clay-Park's Ketoconazole Shampoo, 2%, with the reference listed drug, McNeil Consumer, Inc.'s Nizoral® Shampoo, 2% (formerly manufactured by Janssen Pharmaceutica). The therapeutic success rate was evaluated based on a global assessment, severity score on the clinical signs and symptoms, and the absence of fungal hyphae.

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

2.1

Review of a Bioequivalence Study with Clinical Endpoints

ANDA 76-419
Drug Product: Ketoconazole Shampoo, 2%
Sponsor: Clay-Park Labs, Inc.
Reference Listed Drug: Nizoral® 2% Shampoo (McNeil Consumer), NDA 19927
Reviewer: Carol. Y. Kim, Pharm.D.
Submission dates: May 24, 2002, May 6, 2003
Date of Review: October 29, 2003
V:/firmsam/claypark/ltrs&rev/76419A.mor0502

I. Introduction

Nizoral® (Ketoconazole) 2% Shampoo contains the broad-spectrum synthetic antifungal agent ketoconazole in an aqueous suspension for topical use. It is indicated for the treatment of tinea (pityriasis) versicolor caused by or presumed to be caused by *Pityrosporum orbiculare* (also known as *Malassezia furfur or M. orbiculare*). The approved labeling directs patients to lather and leave the shampoo on the affected damp skin area for 5 minutes and then rinse off with water. One application of the shampoo should be sufficient for the approved indication. The most common adverse events reported with the topical use of Nizoral® (Ketoconazole) 2% Shampoo were pruritus, application site reaction, and dry skin.

Tinea Versicolor

Tinea (pityriasis) versicolor is a non-contagious infection of the skin caused by *Pityrosporum orbiculare (Malassezia furfur)*. This commensal organism is part of the normal skin flora. The condition is often recurrent and may give rise to hyperpigmented or hypopigmented patches on the trunk, which may extend to the neck, arms and upper thighs. Clinical findings result from the rash that presents with small and scaly white-to-pink to tan-to-dark spots and pruritis that is more intense when a person gets hot. Tinea versicolor is common in teenagers or young adults but is rare in the elderly and children. People with oily skin are more susceptible compared to those with naturally dry skin. The appearance of tinea versicolor can be easily recognized by a dermatologist, but the diagnosis is confirmed by microscopic identification for the presence of *Pityrosporum orbiculare*.

II. Background

- The sponsor submitted Bio-IND 15-331 (Ketoconazole Shampoo, 2%) on May 2, 2001. The OGD medical officer consulted with the Division of Dermatologic and Dental Drug Products (DDDDP) regarding appropriate endpoints for the treatment of Tinea Versicolor. Based on their recommendations (August 8, 2001), the OGD medical officer found the sponsor's proposed protocol acceptable and issued the following comments to the sponsor on September 5, 2001:

a. "For the baseline and each follow-up visit, the KOH sample should be taken from the worst and most scaly lesion.
b. For the signs and symptom scoring scale, extent and description of the dermatologic lesions should be described for the categories mild, moderate, and severe.
c. The Global Evaluation should be a static scale describing the extent of and types of lesions associated with each score."

The sponsor initiated this study using the same protocol (#CPL-102, Revision-01) submitted under Bio-IND 15-331. Protocol Amendment #1 dated June 15, 2001 incorporated minor administrative changes to the original protocol.

The current ANDA was submitted on May 24, 2002. On May 6, 2003, the sponsor submitted additional information incorporating this reviewer's requested changes in the data analysis.

- This is a first generic application for Ketoconazole Shampoo, 2%. The OGD recently reviewed one additional protocol #P02-025 [redacted], for Ketoconazole Shampoo.

III. Study Information

Protocol Number: CPL-102, Revision-01

The following review of this protocol includes revisions to the original protocol in italics.

Title: A Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Multi-Center Study To Evaluate The Safety and Bioequivalence of Clay-Park Labs, Inc.'s Ketoconazole Shampoo, 2% and Nizoral® (Ketoconazole) 2% Shampoo in Subjects with Tinea Versicolor

Objective: To demonstrate comparable safety and efficacy of Clay-Park Labs, Inc.'s Ketoconazole Shampoo, 2% (Test Product) and Nizoral® (ketoconazole) 2% Shampoo (Janssen Pharmaceutica; Reference Product) in the treatment of subjects with tinea versicolor in order to establish bioequivalence, and to show superiority of the active treatments over the Clay-Park Labs, Inc. Vehicle (placebo) following a single application of tested products.

Study Design:

This is a randomized, double-blind, parallel-group design comparing the following three products:

1. Test Product: Ketoconazole Shampoo, 2% (Clay-Park Labs, Inc.); Lot #: RX082
2. Reference Product: Nizoral® (ketoconazole) 2% Shampoo (manufactured by Janssen Pharmaceutica); Lot #: 00KL683
3. Vehicle: Ketoconazole Shampoo, 2% - Placebo (Clay-Park Labs, Inc.); Lot #: RX083

Reviewer's Comments: *The RLD (NDA# 19927) is currently distributed by McNeil Consumer Healthcare.*

Study Population:

Healthy Male and Female Patients at least 12 years of age diagnosed with tinea versicolor. Patients must meet the following criteria to be enrolled in the study:

Inclusion Criteria

- Patients or parent/legal guardian provided written Informed Consent, and, if appropriate, child (12-17 years of age) provided assent;
- Must be at least 12 years old or older;
- Must have a total severity score for clinical signs and symptoms of tinea versicolor of at least four ($\geq$4) with at least one sign or symptom rated $\geq$2;
- Must have a diagnosis of tinea versicolor confirmed by a cellophane tape test directed by fluorescence with a Wood's Lamp *or a KOH preparation to detect the presence of fungal hyphae*;
- Must be willing and able to comply with the requirements of the study.

Exclusion Criteria

- Patient and/or guardian has not signed informed consent;
- Is pregnant (urine pregnancy test had to be negative at Visit 1, prior to Randomization) or lactating;
- Has recent history or evidence of other fungal infections, including oral, vaginal or chronic mucocutaneous candidiasis, systemic fungal infections or dermatophyte infections *that could have interfered with assessment of tinea versicolor*;
- Use of systemic antifungal and/or corticosteroid therapy within the 30 days prior to the initiation of study treatment;
- Use of anti-pruritics (e.g., hydrocortisone cream) and/or topical corticosteroid, antifungal, selenium sulfide, or zinc pyrithione preparations within the 14 days prior to the initiation of study treatment, *or used antihistamines that could have interfered with the patient's ability to experience cutaneous sensations within 24 hours prior to the initiation of the study, unless on a stable dose of antihistamine for at least 30 days*;
- Has a history of hypersensitivity or allergy to ketoconazole and/or any of the study medication ingredients;
- Presents with any significant medical conditions that might have placed him/her at increased risk if the test shampoos were used;
- Has participated in any investigational study within the 30 days prior to study initiation;
- Use of any medication that might have interfered with the conduct of the study or placed the prospective patient at increased risk, in the opinion of the investigator.

Study Procedures:

Visit 1: Pretreatment Screening Visit; Baseline and Treatment Day (Day 1)

Once a diagnosis of tinea versicolor was made, the investigator performed a brief physical and general dermatological examination. For all females of childbearing potential, a urine pregnancy test was performed prior to study entry.

Signs and symptoms of tinea versicolor were rated according to a 4-point scale, and the overall severity of tinea versicolor was rated according to the Overall Disease Severity Scale. After satisfying all of the inclusion/exclusion criteria, patients with a total signs and symptoms score ≥ 4, with at least one sign or symptom rated as at least moderate (≥2) were randomly assigned in blocks of five, in a 2:2:1 ratio, to receive one of three study treatments (Test Product, Reference Product, or Vehicle).

Patients were instructed to apply the study medication to all affected areas of the body for 5 minutes on the day/evening of Visit 1 and not to bathe or shower within 4 hours prior to visit 2.

a. General Dermatological Examination

A general dermatological examination was performed with emphasis on the patient's lesions of tinea versicolor. The overall severity of tinea versicolor was rated on a scale of 0 to 3 at the screening visit only as follows:

Overall Disease Severity Scale
0=No scaling, itching or erythema
1=Mild scaling, limited distribution, with or without itching and with or without erythema
2=Moderate scaling, with or without itching
3=Severe, extensive distribution of scaling, with or without itching

b. Evaluation of Clinical Signs and Symptoms of Tinea Versicolor

Signs and symptoms of tinea versicolor were rated at each visit according to a four-point Signs and Symptoms Scale. Only patients with sign and symptom severity scores totaled at least four (≥4), with at least one sign or symptom score of at least moderate (≥2), qualified for the study. To assure consistency, signs and symptoms were rated at the initial visit and at all following visits by the same investigator. The results of these Signs and Symptoms Score determined the clinical response of the study medication.

The following signs and symptoms were rated by the same investigator:

- Erythema
- Pruritus
- Scaling/Desquamation
- Hyper-/Hypopigmentation

Each sign and symptom was rated according to the following four-point scale:

Signs and Symptoms Scale
0=Absent
1=Mild
2=Moderate
3=Severe

c. Cellophane Tape Test/KOH Preparation

Either a cellophane tape test directed by fluorescence with a Wood's Lamp or KOH preparation, was performed to confirm diagnosis of tinea versicolor. The presence or absence of fungal hyphae was examined by the investigator at each visit.

Reviewer's Comments: *In the study amendment dated May 6, 2003, the sponsor provided the detailed description of the KOH and cellophane tape slide preparation techniques. The sponsor reported that an investigator based on the standard clinical practices employed at his/her investigative center utilized the specific technique. For Transparent Tape Slide Prep Technique (Cellophane Tape Test), the investigator was instructed to select an active lesion site by performing Wood's lamp examination (check for pale yellow fluorescence of active lesions). After cleaning the sample site with a 70% alcohol swab and drying with gauze, the adhesive side of a 1 1/2" piece of transparent tape was firmly pressed against the prepared specimen site. Then, the tape was stripped from the site and placed on a glass microscope slide. The presence of suspected fungal structures was confirmed using the high/dry (40X) objective.*

Visit 2: Post-Treatment (Day 2-5); Safety Evaluation

Patients returned for an evaluation two to five days after receiving the study medications (Day 2-5). This visit was primarily designed for assessment of safety. The investigator rated the signs and symptoms of tinea versicolor, performed a cellophane tape test/KOH preparation, and ascertained changes in general health, medical history, and concomitant medications. The investigative staff evaluated patient compliance and retrieved the empty bottle of study medication.

Visit 3: Post-Treatment (Day 8-10); Safety Evaluation

Patients returned for an evaluation eight to ten days after receiving the study medication (Day 8-10). This visit was primarily designed for evaluation of safety and supportive efficacy. The investigator rated the signs and symptoms of tinea versicolor, performed a Physician's Global Assessment, performed a cellophane tape test/KOH preparation, and ascertained changes in general health, medical history, and concomitant medications. The investigative staff confirmed that the patient had not bathed or showered within 4 hours prior to the visit, retrieved the empty bottle of study medication (if not returned at the previous visit), and confirmed other study procedures.

The Physician's Global Assessment (PGA) was graded on a scale of 1 to 5 as follows:

Physician's Global Assessment Scale
1=Healed (all visual evidence of mycotic disease has disappeared with the exception of hyper-/hypopigmentation)
2=Markedly improved (mild residual scaling and possible hyper- and/or hypopigmentation)
3=Considerable residual lesions/scaling
4=No change
5=Worsening

Visit 4: Post-Treatment Final Visit (Day 29-33); Primary Endpoint Evaluation Day

Patients returned for an evaluation twenty-nine to thirty-three days after receiving the study medications (Day 29-33). This visit was designed for the evaluation of therapeutic response and safety. The investigator rated the signs and symptoms of tinea versicolor, performed a Physician's Global Assessment, performed a cellophane tape test/KOH preparation, and ascertained changes in general health, medical history, and concomitant medications.

Occurrence of adverse events was solicited, changes in concomitant medications were recorded, and compliance was checked. The bottle of used and unused study medication was retrieved at this visit if it was not returned at the previous visit.

Evaluation of Clinical Response

The primary efficacy variable was the proportion of patients in each treatment group with a therapeutic success at the Day 31 visit. The secondary efficacy variable was the proportion of patients in each treatment group with a therapeutic success at the Day 8 visit. Therapeutic success was defined as follows:

1. a Global Evaluation of "healed" (1); and
2. a severity score on the Clinical Signs and Symptoms of:
    a. Zero (0) for Erythema, and
    b. Zero (0) for Pruritus, and
    c. Zero (0) for Scaling/Desquamation, and
    d. Less than or equal to two ($\leq$2) for Hyper-/Hypopigmentation; and
3. *the absence of fungal hyphae, as demonstrated by a cellophane tape test directed by fluorescence with a Wood's Lamp or KOH preparation.*

The active treatment groups were also evaluated to determine if their success rates were statistically superior to that of the Vehicle (Placebo) at the Day 31 visit in the ITT population. A Last Observation Carried Forward (LOCF) approach was used for missing data in all ITT analyses.

Population Analysis

Intent-to-treat (ITT): patients who completed baseline visit, applied the study medication, and had at least one post-baseline study evaluation

Per-protocol (PP): patients who had met all inclusion/exclusion criteria, applied the study medication as directed, had been assessed for success/failure at the relevant visit, and had no study protocol violations that could have altered the effect of or the accurate assessment of the applied study medication.

Safety:

Safety was to be assessed by recording the adverse events during the study from visits 2 through 4. The frequency of adverse events was to be tabulated by treatment group, body system, severity, and relationship to study medication.

Concomitant Medications:

Except for the occasional use of analgesics, such as aspirin, acetaminophen, ibuprofen, or medications for the treatment of seasonal disease (cold, flu etc...), no new medication were to be taken during the 31-day study period. Patients were to be permitted to take medication necessary for their health if they had been at stable dose for the preceding 30 days.

Statistical Plan:

Primary Endpoint

The determination of bioequivalence was to be evaluated based on therapeutic success rates of the test and reference products at the Day 31 visit. Each active treatment was also to be evaluated to determine if its success rate is statistically superior to that of the vehicle (placebo) at the Day 31 post-treatment visit.

Reviewer's Comments:

- *The sponsor's proposed primary endpoint is cure (therapeutic success) rates in the PP population at Day 31 visit.*
- *To demonstrate that the study is sufficiently sensitive to show a difference between products, both the test and reference products should be superior to the vehicle group at Day 31 visit in the ITT population.*
- *Proportional difference in cure rates at Day 8 visit in the PP population may be evaluated as a secondary endpoint.*

Sample Size

A minimum of 335 evaluable patients, 134 per each active treatment group and 67 on placebo group, were to be selected for this study. To accommodate an estimated drop-out rate of approximately 30%, the study was to enroll 500 patients. Patients with either protocol violations or deviations were not discontinued from the study, unless, in the investigator's clinical judgment, continuation in the study could be deleterious to the patient's health or well being. This was calculated to provide 0.85 probability that the 90% continuity-corrected confidence interval, on the difference between test and reference cure rates, would fall in the interval between (+0.20 and –0.20). The test and reference efficacy rates would be also shown to be statistically superior (α=0.05, two-sided) to that of the vehicle.

Analysis

The demographic variables of each treatment group at baseline were to be compared to ensure comparability of the groups. Continuous variables were to be examined by analysis of variance or by the nonparametric Fridman's ANOVA. Categorical variables such as gender, and race were to be examined by Chi square test or Fisher's exact test.

Evaluable patients must meet the Inclusion/Exclusion Criteria, receive the study treatment, and not have any protocol violations that would prejudice the outcome assessment. In addition, they must have been assessed for cure or failure (therapeutic success/failure) at the Day 31 visit.

IV. RESULTS

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Study Centers and Investigators:

Center # (no. of patients)	Principal Investigator and Address	Center # (no. of patients)	Principal Investigator and Address
01 (19)		15 (20)	
02 (20)		17 (15)	
03 (25)		19 (35)	
05 (19)		20 (10)	
06 (25)		21 (15)	
07 (15)		22 (5)	
08 (15)		23 (24)	
09 (25)		24 (15)	
5)		25 (15)	
11 (15)		26 (20)	
12 (15)		27 (25)	
13 (65)		28 (20)	

Study Period: July 25, 2001- February 27, 2002

Patient Enrollment:

A total of 501 patients were enrolled in the study; 202 in the test group (Clay-Park), 198 in the reference group (McNeil Consumer), and 101 in the vehicle group. Of these, six patients had no post-baseline visit and were excluded from the ITT population analyses by the sponsor. The remaining 495 patients (199 in the test, 196 in the reference, and 100 in the vehicle) were treated and included in the ITT population analyses. The distribution of patients per treatment arm for each analysis population is shown in Table I.

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

Population	Clay-Park N	McNeil N	Vehicle N	Total N
Enrolled	202	198	101	501
*no post-baseline visit data	-3	-2	-1	-6
^Intent-to-Treat (ITT)	199	196	100	495
**Did not complete the study because patient				
1) refused to continue	-1	-1	0	-2
2)lost to follow-up	-5	-2	-1	-8
3) had surgery appt.	0	-1	0	-1
4) used Nizoral® cream	-1	0	0	-1
Evaluation for presence of fungal hyphae not performed at Visit 4	-1	-1	-2	-4
***Prohibited medication use	-5	-2	-1	-8
****Outside visit window (OVW) for Visit 4	-2	-1	0	-3
Violated In/Ex criteria	-1	-2	-2	-5
Took shower or bath 4 hours prior to Visit 4	0	-3	-1	-4
Did not comply with protocol	0	-3	-1	-4
^^Evaluable Population (EP)	183	180	92	455

*T: 29 (3), 71 (9), 288 (20); Ref: 32 (3), 630 (28); V: 225 (27)
**1) T: 627 (28); Ref: 34 (3)
2) T: 230 (27), 196 (24), 306 (28), 448 (1), 466 (22); Ref: 94 (12), 53 (6); V: 126 (19)
3) Ref: 67 (9)
4) T: 528 (7)
***T: 35 (3), 10 (10), 16 (10), 234 (27), 543 (27); Ref: 412 (5), 90 (12), 292 (20); V: 44 (6)
****OVW (-5 days to +7 days); T: 131 (19), Day 42; 184 (24), Day 22; Ref: 616 (3), Day 24

^Included all patients who received 1 application of the study medication and complete at least one post treatment visit.
^^Completed 1 application of the study medication, had no significant protocol violation, and returned within the acceptable visit windows (-5 days to -7 days) for Day 31 evaluation.

Reviewer's comments:
The sponsor excluded patients from the Day 31 PP population if they a) did not complete at least visit 2, b) were out-of-visit window (+/- 2 days) for Day 8 or Day 31 visits, c) missed Day 8 or Day 31 clinical and mycological evaluation, d) completed dermatological assessment by non-board certified dermatologist or a different investigator, e) took shower 4 hours prior to Day 8 or Day 31 visits and f) were non-compliant with the protocol. For those who completed the study, the visit window for the Day 31 evaluation ranged from -11 days to +12 days.

1) *The sponsor excluded a total of 131 patients from the Day 31 Per Protocol (PP) analyses due to minor protocol deviations. Since a large number of patients were excluded from the final analysis due to protocol deviations that are considered minimal and not likely to impact the outcome of the study, this reviewer concludes that it is not necessary to exclude them for the following reasons:*

- *The sponsor excluded almost 8.2% (41/495) of patients from the Day 31 PP population analysis because they proposed too narrow visit window (+/-2 days) for the follow-up visit. Excluding these many patients may impact the evaluation of bioequivalence between two active treatments. Considering the nature of disease process of tinea versicolor, the single-dose treatment, and a wider visit window accepted in the innovator's NDA study, a wider visit window for Visit 4 (follow-up) is appropriate.*

  The innovator's Nizoral® 2% Shampoo (NDA 19927) demonstrated a high degree of clinical efficacy against tinea versicolor without the need for maintenance therapy for up to 4 weeks (-5 days to +7 days) after treatment (KET-USA-34). In addition, supportive clinical trial (Meisel et. al) conducted in Germany demonstrated clinical efficacy of innovator's product against tinea versicolor when patients were evaluated up to 60 days after a single treatment. Still 75% of patients that were followed up to 60 days demonstrated consistent clinical and mycological cure. Since the primary endpoint for this product is a follow-up visit (Day 31) and clinical response against tinea versicolor is well-maintained beyond 4 weeks post-treatment, extending visit windows similar to the innovator's study (–5/+7 days) capturing more evaluable patients is appropriate.

- *The sponsor also excluded 6.5% of (32/495) patients from the evaluable population because either a non-board certified dermatologist or a different investigator, in the absence of the primary investigator, examined them. The study protocol is designed to have the same investigator perform dermatological assessments throughout the study. However, it is not necessary to exclude these patients from the evaluable population because [redacted] (non-board-certified dermatologist) performed the dermatological assessment. [redacted] is a principal investigator for the clinical site #1 and has received sufficient training (professor in dermatology department) to conduct simple dermatological assessment.*

In addition, dermatological assessments made by other investigators in the absence of the principal investigator are not likely to interfere with the outcome of the study. It is generally recommended to blind the investigator from the baseline scores to minimize bias. Only the evaluation of the Physician's Global Assessment scale would likely be affected by a different investigator. A static scoring system that does not depend on change from baseline is usually recommended for such scale. However, in this case, the score that was accepted for a clinical success was consistent with complete clearing and can be evaluated by a different investigator.

- *Therefore, the following patients that were previously excluded by the sponsor should be included in the Evaluable (EP) population analysis:*

Reason for inclusion at EP population analysis (Day 31 visit)	Test Patient number (center)	Reference Patients number (center)	Vehicle Patient number (center)
Visit window acceptable (VWA)	442 (1), 401 (5) , 43 (6), 525 (7), 535 (7), 241 (8), 482 (9), 348 (11), 91 (12), 369 (15), 371 (15), 394 (17), 576 (19), 142 (21), 165 (23), 512 (23), 207 (25), 267 (26), 270 (26), 553 (26), 545 (27), 315 (28)	41 (6), 13 (10), 370 (15), 556 (15), 560 (15), 571 (19), 166 (23), 206 (25), 268 (26), 229 (27), 542 (27), 308 (28), 313 (28)	324 (2), 620 (3), 345 (10), 504 (14), 364 (15), 580 (19), 213 (25), 272 (26), 280 (26), 544 (27)
Different investigator acceptable (DIA)	496 (14) , 498 (14), 503 (14), 382 (17), 383 (17), 386 (17), 390 (17), 395 (17), 144 (21), 518 (23)	244 (8), 497 (14), 502 (14) 387 (17), 385 (17), 389 (17), 391 (17), 393 (17), 563 (19) 145 (21), 161 (23), 162 (23), 513 (23), 519 (23)	499 (14), 388 (17), 146 (21), 511 (23)
Principal investigator: Non-board dermatologist (Dr. Ali)	508 (1)	441 (1), 507 (1)	509 (1)
Missing visit 2 or 3 doesn't' interfere; Visit 4 data available	25 (3), 55 (6)	27 (3), 613 (3)	-
Clinical outcome not significantly altered by concomitant med. use	405 (5)[1]	7 (10)[2]	-
Non-compliance apply only to visit 3; Visit 4 data available	406 (5)	-	-

1Patient #405 (center 5) started on a new medication (Remeron®) prior to Visit 4 (Day 31). Since the primary endpoint of this study requires the absence of the fungal hyphae and complete clinical response, this reviewer concludes that the possible drug-related effect of its use on the study outcome is not likely to be clinically significant.

[2] Patient #7 (center 10) was on a short-term antibiotic (cephalexin®) use prior to Visit 4. Since this systemic antibiotic is not known to cause clinical effect, and the complete eradication of Tinea Versicolor require topical antifungal product, it is inappropriate to exclude this patient from the evaluable population. So, should include this patient in the evaluable population analysis.

2) *Patient #35 (center 3; Test) received prohibited medication (diphenhydramine) one day prior to Day 31 evaluation but the sponsor included this patient in the PP population analysis. Due to violation of the protocol, this patient should be excluded from the Day 31 evaluable population analysis.*

Demographics:

Out of 501 patients enrolled in the study, 284 (57%) male and 211 (43%) female patients were included in ITT population. Of the 495 ITT patients, 423 (85%) were White, 25 (5%) were Black, 38 (8%) were Hispanic, 2 (0.4%) were Asian, and 7 (1%) were described as others. The baseline demographics, age, gender, and race were comparable and not statistically different in all treatment groups in the ITT population. The mean age was 33 (14.6-67.6), 36 (12.2-77.1), and 35 (15.2-69.5) years for the test, reference, and placebo products, respectively. See Table II for the demographic characteristics for the ITT population.

TABLE II – DEMOGRAPHIC CHARACTERISTICS FOR INTENT-TO-TREAT PATIENTS

Parameter	Ketoconazole Shampoo, 2% (N=199)	Nizoral® (ketoconazole) 2% Shampoo (N=196)	Vehicle (N=100)	p-value
Gender(n,%)				
Male	113 (57%)	119 (61%)	52 (52%)	0.340[1]
Female	86 (43%)	77 (39%)	48 (48%)	
Race(n,%)				
White	175 (88%)	163 (83%)	85 (85%)	0.303[1]
Black	10 (5%)	9 (5%)	6 (6%)	
Hispanic	12 (6%)	17 (9%)	9 (9%)	
Asian	0 (0%)	2 (1%)	0 (0%)	
Other	2 (1%)	5 (3%)	0 (0%)	
Age(years)				
Mean ± SD	33.26 ± 12.26	35.63 ± 13.76	35.08 ± 12.47	0.469[2]
Min - Max	14.6 - 67.6	12.2 - 77.1	15.2 - 69.5	

[1]P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site. For the variable race, the p-value was calculated after combining the following categories: Black, Hispanic, Asian, and Other.
[2]P-values for treatment comparisons from Friedman's test with factors of treatment and site.

Baseline Disease Severity:

The Sponsor tabulated the baseline dermatological assessments for clinical signs and symptom scores, including erythema, pruritus, scaling/desquamation, and hyper-/hypopigmentation, and overall severity of tinea versicolor. As shown in Table III, mean clinical signs and symptom scores and overall severity of disease scores were not statistically different between treatments in the ITT population at baseline visit. All 495 patients had fungal hyphae present at baseline visit.

TABLE III – DERMATOLOGICAL ASSESSMENTS AT BASELINE (DAY 1) FOR INTENT-TO-TREAT PATIENTS

Parameter	Ketoconazole Shampoo, 2% (N=199)	Nizoral® (ketoconazole) 2% Shampoo (N=196)	Vehicle (N=100)	p-value
Signs and Symptoms Scores				
Total				
Mean ± Std	6.14 ± 1.65	6.13 ± 1.59	6.12 ± 1.53	0.934[1]
Min - Max	4.0 - 11.0	4.0 - 11.0	4.0 - 11.0	
Erythema				
Mean ± Std	1.31 ± 0.88	1.36 ± 0.83	1.43 ± 0.89	0.629[1]
Min - Max	0.0 - 3.0	0.0 - 3.0	0.0 - 3.0	
Pruritus				
Mean ± Std	0.93 ± 0.96	0.85 ± 0.84	0.77 ± 0.90	0.144[1]
Min - Max	0.0 - 3.0	0.0 - 3.0	0.0 - 3.0	
Scaling/Desquamation				
Mean ± Std	1.93 ± 0.58	1.95 ± 0.64	2.00 ± 0.64	0.593[1]
Min - Max	1.0 - 3.0	0.0 - 3.0	1.0 - 3.0	
Hyper-/Hypopigmentation				
Mean ± Std	1.97 ± 0.68	1.97 ± 0.73	1.92 ± 0.72	0.692[1]
Min - Max	0.0 - 3.0	0.0 - 3.0	0.0 - 3.0	
Overall Severity of Tinea Versicolor				
Mean ± Std	2.16 ± 0.64	2.15 ± 0.62	2.11 ± 0.55	0.932[1]
Min - Max	1.0 - 3.0	1.0 - 3.0	1.0 - 3.0	
Fungal Hyphae				
Presence	199 (100%)	196 (100%)	100 (100%)	1.000[2]
Absence	0 (0%)	0 (0%)	0 (0%)	

[1]P-values for treatment comparisons from Friedman's test with factors of treatment and site.
[2]P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, adjusted for site.

Efficacy Outcomes:

The Sponsor's primary and secondary analyses of therapeutic success (clinical success and absence of fungal hyphae) at Day 8 and Day 31 visits for the PP population are shown in Table IV and V. The 90% CI for the cure rate comparing the test and the reference products at the Day 31 (primary endpoint) visit for the PP population is tabulated in Table IV. The sponsor used Wald's method with Yate's continuity correction for the calculation of the 90% CI.

TABLE IV - PRIMARY EFFICACY ANALYSIS

	Ketoconazole Shampoo, 2%	Nizoral® (ketoconazole) 2% Shampoo	Vehicle	90% CI for Bioequivalence of Ketoconazole Shampoo, 2% to Nizoral® (ketoconazole) 2% Shampoo	p-values: Ketoconazole Shampoo, 2% vs. Vehicle	p-values: Nizoral® (ketoconazole) 2% Shampoo vs. Vehicle
Day 31 Per-Protocol Patients (n,%)						
Day 31	(N=146)	(N=147)	(N=77)			
Success	89 (61%)	91 (62%)	8 (10%)	-10.98% to 9.09%[1]		
Failure	57 (39%)	56 (38%)	69 (90%)			
Intent-to-Treat Patients (n,%)						
Day 31	(N=199)	(N=196)	(N=100)			
Success	121 (61%)	115 (59%)	10 (10%)		<0.001[2]	<0.001[2]
Failure	78 (39%)	81 (41%)	90 (90%)			

[1]Confidence interval calculated using Wald's method with Yate's continuity correction.
[2]P-values for treatment comparisons from two-sided Z-test with Yate's continuity correction.

TABLE V – SECONDARY EFFICACY ANALYSIS

	Ketoconazole Shampoo, 2%	Nizoral® (ketoconazole) 2% Shampoo	Vehicle	90% CI for Bioequivalence of Ketoconazole Shampoo, 2% to Nizoral® (ketoconazole) 2% Shampoo	p-values: Ketoconazole Shampoo, 2% vs. Vehicle	p-values: Nizoral® (ketoconazole) 2% Shampoo vs. Vehicle
Day 8 Per-Protocol Patients (n,%)						
Day 8	(N=162)	(N=169)	(N=85)			
Success	19 (12%)	8 (5%)	5 (6%)	1.44% to 12.55%[1]		
Failure	143 (88%)	161 (95%)	80 (94%)			
Intent-to-Treat Patients (n,%)						
Day 8	(N=199)	(N=196)	(N=100)			
Success	23 (12%)	14 (7%)	5 (5%)		0.104[2]	0.645[2]
Failure	176 (88%)	182 (93%)	95 (95%)			

[1]Confidence interval calculated using Wald's method with Yate's continuity correction.
[2]P-values for treatment comparisons from two-sided Z-test with Yate's continuity correction.

Reviewer's comment: *The sponsor's analyses show that the 90% CI of the proportional difference in the cure rates (therapeutic success) between the test and the reference products at the follow-up visit (Day 31; primary endpoint) is within (-.20, +.20) . The test and reference*

products were both significantly superior over the placebo group ($p<0.001$) for the cure rate at the Day 31 visit. Because the sponsor excluded a large number of evaluable patients from the per protocol population, this reviewer asked the sponsor to perform a separate statistical analysis incorporating 81 additional patients that were excluded by the sponsor into the PP population (Visit 4). The result of the sponsor's reanalysis (see Study Amendment dated 5/6/03) in the evaluable population was consistent (-7.57, 10.38) with the result shown in Table IV. A statistical analysis was requested to verify the sponsor's reanalysis.

Adverse Events:

No death occurred during the study. A total of 115 adverse events were reported in the study (49 test; 42 ref; 24 placebo). The sponsor's analysis of adverse events by the body system is shown below in Table VI. This reviewer used the sponsor's data, Listing 14 (adverse events), to tabulate the frequency of adverse events by the severity in Table VII.

The sponsor identified 24 patients (11/199 test; 7/196 ref; 6/100 placebo) with skin-related adverse events. Regarding the occurrence of skin related adverse events, there was no significant statistical difference between two active treatments ($p=0.330$). The summary of skin-related adverse events was tabulated by this reviewer in Table VIII. More patients experienced burning at the application site in the test product compared to the reference product, and more patients experienced itching at the application site in the reference product compared to the test product.

Except for four severe events related to application site reactions such as itching and redness in the reference and vehicle groups, all other adverse events (skin-related or not) were reported to be mild to moderate.

One patient [T: 81 (12)] experienced a serious adverse event that was considered unrelated to the study medication. A 65 years old white male was enrolled into the study on 9/14/01 with pre-existing melanoma on left arm. The principal investigator conducted a general dermatological examination and excised an irregular mole from the patient's left arm. The biopsy revealed that the lesion was invasive melanoma and was re-excised on 9/14/01. The patient's x-ray on 9/18/01 showed no evidence of acute disease and no metastatic disease. This patient completed the study per protocol and no further complication was seen at the follow-up visit.

Table VI: Summary of Adverse Events by Body System for Skin and Non-Skin Related Events

	Ketoconazole Shampoo, 2% (N=199)	Nizoral® (ketoconazole) 2% Shampoo (N=196)	Vehicle (N=100)
Body System[1]			
BODY AS A WHOLE	17 (8.5%)	17 (8.7%)	8 (8.0%)
ABDOMINAL PAIN	0 (0%)	1 (0.5%)	0 (0%)
ALLERGIC REACTION	0 (0%)	3 (1.5%)	0 (0%)
FEVER	2 (1.0%)	1 (0.5%)	0 (0%)
HEADACHE	10 (5.0%)	7 (3.6%)	3 (3.0%)
INFECTION	4 (2.0%)	2 (1.0%)	2 (2.0%)
INJURY ACCIDENTAL	1 (0.5%)	3 (1.5%)	1 (1.0%)
MALAISE	0 (0%)	0 (0%)	1 (1.0%)
PAIN	1 (0.5%)	1 (0.5%)	1 (1.0%)
CARDIOVASCULAR SYSTEM	0 (0%)	1 (0.5%)	0 (0%)
MIGRAINE	0 (0%)	1 (0.5%)	0 (0%)
DIGESTIVE SYSTEM	4 (2.0%)	1 (0.5%)	0 (0%)
ABSCESS PERIODONTAL	1 (0.5%)	0 (0%)	0 (0%)
DIARRHEA	1 (0.5%)	0 (0%)	0 (0%)
DYSPEPSIA	1 (0.5%)	0 (0%)	0 (0%)
GASTROENTERITIS	1 (0.5%)	0 (0%)	0 (0%)
ULCER MOUTH	0 (0%)	1 (0.5%)	0 (0%)
MUSCULOSKELETAL SYSTEM	0 (0%)	1 (0.5%)	0 (0%)
MYALGIA	0 (0%)	1 (0.5%)	0 (0%)
NERVOUS SYSTEM	1 (0.5%)	1 (0.5%)	0 (0%)
ANXIETY	0 (0%)	1 (0.5%)	0 (0%)
INSOMNIA	1 (0.5%)	0 (0%)	0 (0%)
RESPIRATORY SYSTEM	9 (4.5%)	5 (2.6%)	3 (3.0%)
BRONCHITIS	0 (0%)	1 (0.5%)	0 (0%)
COUGH INCREASED	1 (0.5%)	0 (0%)	0 (0%)
LARYNGITIS	0 (0%)	1 (0.5%)	0 (0%)
PHARYNGITIS	3 (1.5%)	3 (1.5%)	2 (2.0%)
RHINITIS	3 (1.5%)	0 (0%)	1 (1.0%)
SINUSITIS	3 (1.5%)	1 (0.5%)	1 (1.0%)
SKIN AND APPENDAGES	11 (5.5%)	7 (3.6%)	6 (6.0%)
ACNE	0 (0%)	1 (0.5%)	1 (1.0%)
ALOPECIA	1 (0.5%)	0 (0%)	0 (0%)
APPLICATION SITE REACTION	6 (3.0%)	4 (2.0%)	2 (2.0%)
HERPES SIMPLEX	1 (0.5%)	0 (0%)	0 (0%)
MELANOMA SKIN	1 (0.5%)	0 (0%)	0 (0%)
PRURITUS	1 (0.5%)	1 (0.5%)	4 (4.0%)
RASH	1 (0.5%)	1 (0.5%)	1 (1.0%)
SKIN DRY	1 (0.5%)	0 (0%)	1 (1.0%)
SPECIAL SENSES	0 (0%)	2 (1.0%)	0 (0%)
EAR PAIN	0 (0%)	2 (1.0%)	0 (0%)
UROGENITAL SYSTEM	1 (0.5%)	1 (0.5%)	1 (1.0%)
DYSMENORRHEA	0 (0%)	0 (0%)	1 (1.0%)
DYSURIA	1 (0.5%)	0 (0%)	0 (0%)
URINARY TRACT INFECTION	0 (0%)	1 (0.5%)	0 (0%)

[1]Counts reflect numbers of patients in each treatment group reporting one or more adverse events that map to the COSTART 5th edition body system. At each level of summarization (body system or event) patients are only counted once. Percentages of patients in each treatment group are also given.

Table VII. Adverse Events by Severity and Relationship for Skin and Non-Skin Related Events (per reviewer)

Severity	Test	Reference	Vehicle
Mild	35	22	19
Moderate	14	17	4
Severe	0	3	1
Total	49	42	24

Table VIII. Frequency of skin-related adverse events (per reviewer)

Adverse Events	Test (n=199)	Reference (n=196)	Vehicle (n=100)
Application site reactions:			
1) Reddened dots	1	0	0
2) Burning	6	0	0
3) Dryness	2	0	1
4) Rash	0	1	0
5) Pruritus	0	4	2
Melanoma	1	0	0
Pruritus (body)	1	0	3
Alopecia	1	0	0
Rash	1	1	0
Acne	0	1	0
Herpes simplex	1	0	0
Total number of skin-related AE	14	7	6
Total number of patients with skin-related AE	11 (5.5%)	7 (3.6%)	6 (6%)

Reviewer's comments: *The overall percentage of patients with skin-related adverse events was less than 7% in all three groups similar to the incidence reported in the innovator's study (KET-USA-34).*

V. Formulation

The composition of Clay-Park's Ketoconazole Shampoo, 2%, is provided below (vol. 1.6, p. 2866).

Ingredients	% (w/w)
Ketoconazole USP	
Hydrochloric Acid NF	
Sodium Hydroxide NF	
FD&C Red #40	
(PEG-120 Methyl Glucose Dioleate)	
(Laurdimonium Hydroxypropyl Hydrolyzed Collagen)	
(Coconut Fatty Acid Diethanolamide)	
(Imidurea NF)	
(Sodium Lauryl Ether Sulfate)	
(Disodium Laureth Sulfosuccinate)	
Purified Water USP	
Sodium Chloride USP	

*The amount of Ketoconazole includes excess [i.e.

The Chemistry review indicates that the use of overage of active ingredient is acceptable. The sponsor claimed that the quantities of all of the inactive ingredients in their formulation were confirmed with the FDA via telephone conversations dated from 4/17/00 to 9/14/00 as listed in vol. 1.1 (page 21).

Retention Samples

According to the study report, provided the blinding, labeling, assembly and shipment of study medication to the study sites. They also stored the retention samples that were randomly selected by the site investigator as directed at their facility.

VI. Review of Division of Scientific Investigation (DSI) report (July 2, 2003)

The DSI has completed the clinical site inspection and recommended that the study CPL-102 be accepted for the review. The DSI noted the following patients to be out of visit window for Visits 3 and 4:

Visit 3: #579
Visit 4: #131, 576, 571, 580

Reviewer's Comments: *The sponsor already excluded patients #131 and #579 from the evaluable population due to revisits outside of the visit window and non-compliance with the protocol. Patients #576, 571 and 580 are considered to be within the acceptable visit window (-5/+7 days) for the evaluation as explained by this reviewer in details above. Therefore, based on the DSI final report, no further adjustment for the evaluable population was needed.*

VII. Review of the FDA Statistical Report (10/17/03)

The conclusion of the FDA statistical analysis supports the bioequivalence of the test and the reference products. The 90% CI of the therapeutic success rate for the evaluable population at the primary endpoint (day 31, visit 4) was within -.20 and +.20. The test and the reference products were also shown to be significantly superior to the placebo/vehicle (p</=0.001) at visit 4 in the ITT population.

Based on this reviewer's comments above, the FDA statistician provided the summary of the equivalence test for the evaluable population as shown below, and their conclusion is consistent with the sponsor's results.

Primary endpoint: Therapeutic success rate at visit 4 (Day 31)

Efficacy and equivalence analyses for primary endpoint

Population	Test* % successes (no. of successes/total number)	Reference* % successes (no. of successes/total number)	Placebo* % successes (no. of successes/total number)	P-value# for test vs. placebo	P-value# for Reference vs. placebo	90% CI for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
	60.8 (121/199)	58.7 (115/196)	10.0 (10/100)	<0.001	<0.001		
EP	62.6 (114/182)	61.1 (110/180)	8.8 (8/91)			-7.4, 10.5	Yes

*:The rate of success equals the number of successes divided by the total number, then multiplied by 100.
#:The p-values were from Fisher's exact test (1-sided).

The statistician identified a total of 453 evaluable population, 182 for the test, 180 for the reference, and 91 for the vehicle/placebo group. The additional two patients from the test and vehicle groups were excluded from the evaluable population by the statistician for the following reasons:

1. Patient #345 (11) from the vehicle group was excluded due to completion of visit 4 (day 39) outside of the acceptable range.

2. Patient #405 (5) was originally excluded from the evaluable population by the sponsor due to the initiation of the new medication (Remeron®) during the study. Since the primary endpoint of this study requires the absence of the fungal hyphae and complete clinical response, this reviewer concluded that this patient should be included in the evaluable population. When this patient's data are included in the evaluable population, the 90% CI for the test and the reference products is still within -.20 and +.20 (-0.068, 0.11)[1] based on this reviewer's calculation. Therefore, the outcome of the study remains the same.

[1] based on number of successes/total number of 115/182 (test) vs. 110/180 (reference) in the evaluable population at visit 4 (day 31).

The secondary endpoint (therapeutic success at visit 3, day 8) analysis also demonstrated that the 90% CI of the therapeutic success rate for the test and the reference products were within -0.20 and +0.20. Only the test product demonstrated the superiority over the placebo/vehicle group at visit 3.

VIII. Conclusion

The data presented in this ANDA demonstrate that Clay-Park Labs, Inc.'s Ketoconazole Shampoo, 2%, is bioequivalent to the reference listed drug, Nizoral® Shampoo, 2%. The FDA statistical review confirms that the 90% CI of the proportional difference in therapeutic success rates between the test and reference products at visit 4 (day 31; primary endpoint) is within (-.20, +.20). The therapeutic success rate was evaluated based on a global assessment, severity score on the clinical signs and symptoms, and the absence of fungal hyphae.

IX. Recommendation

The data submitted to ANDA 76-419, using the primary endpoint of therapeutic success rate at the follow-up visit (day 31, visit 4), are adequate to demonstrate bioequivalence of Clay-Park Labs, Inc.'s Ketoconazole Shampoo, 2%, with the reference listed drug, McNeil Consumer, Inc.'s Nizoral® Shampoo, 2% (formerly manufactured by Janssen Pharmaceutica).

Carol Y. Kim

10/29/03

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

Date

Dena R. Hixon MD

10/29/03

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

Date

Dale P. Conner

11/4/03

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

Date

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-419 SPONSOR : Clay-Park Labs. Inc.

DRUG AND DOSAGE FORM : Ketoconazole Shampoo, 2%

STRENGTH(S) : 2%

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status: completed on 7/2/03	Inspection results: acceptable
First Generic _____ New facility _____ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

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

INITIAL : _____ DATE : 10/29/03

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

INITIAL : DRH DATE : 10/29/03

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

INITIAL : _____ DATE : 11/4/03

CC: ANDA 76419
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ C.Kim
HGD-600/ D. Hixon

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Endorsements: (Final with Dates)
HFD-600/C. Kim CW 10/29/03
HFD-600/D. Hixon DRH 10/29/03
HFD-650/D. Conner 11/4/03

BIOEQUIVALENCY - ACCEPTABLE

submission dates:
May 24, 2002
May 6, 2003

1. Bioequivalence Study (STU); May 24, 2002 Strengths: 2%
Outcome: AC

2. Study Amendment (STA); May 6, 2003 Outcome: AC

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

* Please close the above pieces for both reviewers listed.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-419

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

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

DATE : July 2, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 02-JUL-2002

SUBJECT: Examination of the bioequivalence study with clinical endpoints submitted with an ANDA for Ketoconazole Shampoo, 2% to determine if the application is substantially complete for filing.

Clay-Park Labs. Inc. has submitted ANDA 76-419 for Ketoconazole Shampoo, 2%. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the Bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the bioequivalence study with clinical endpoints submitted by Clay-Park on May 24, 2002 for its Ketoconazole product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

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

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

Reference is made to the deficiency letter faxed on November 15, 2002. Ms. Edwards called with regards to a general question about regulatory issues. The call was precipitated by deficiency #8.

Please provide an alternate validated method and specification for quantitation of the ——— imidurea, for the product release and stability.

The agency responded by citing a reference from the following article:

[redacted]

Ms. Edwards was advised to cantact Wanda Pamphile, if she should have any further questions.

APPEARS THIS WAY
ON ORIGINAL

DATE:
December 3, 2002

ANDA NUMBER: 3.1
76-419

PRODUCT NAME:
Ketoconazole Shampoo 2%

INITIATED BY:

Firm __X__ **Agency**___

FIRM NAME:
Clay-Parks Labs, Inc.

FIRM REPRESENTATIVE:
Candace Edwards

TELEPHONE NUMBER:
(718) 960-9976

FDA REPRESENTATIVE:
Paul Schwartz, Ph.D.
Shing Liu, Ph.D.
Benjamin Lim, Ph.D.
Wanda Pamphile, Pharm. D.

SIGNATURE

Paul Schwartz, Ph.D. RS 12/3
Shing Liu, Ph.D. S.H. Liu 12/3/02
Benjamin Lim, Ph.D. BL 12/4/02
Wanda Pamphile, Pharm. D. WP. 12/3

Orig: ANDA 76-419
Cc: Division File
Chem. I telecon binder

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MEMORANDUM

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

DATE: July 2, 2003

FROM: Tamal K. Chakraborti, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 7/29/03
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering ANDA 76-419, Ketoconazole Shampoo, 2%, sponsored by Clay-Park Labs, Inc./Agis Group

TO: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence(HFD-650)

At the request of HFD-650, the Division of Scientific Investigations conducted an audit of the following bioequivalence study for ANDA 76-419:

Protocol CPL-102: A multicenter, double-blind, randomized, parallel group, placebo-controlled study comparing Clay-Park's Ketoconazole Shampoo 2% to Janssen's Nizoral® (Ketoconazole) 2% in patients with tinea versicolor.

This study involved a total of 25 individual sites. The following three sites were selected for inspection based on the maximum number of enrolled patients.

Following the inspections of these sites, Form FDA 483 was issued at each site. The objectionable items and our evaluations of the findings are listed below:

1. **Lack of records to confirm batch/lot number of the test, reference and placebo drug products used in this study.**

Batch/lot numbers were not found in drug receipt records. The site responded (dated 4/29/03) that the sponsor maintained batch/lot numbers of the study medications used in this study. The sponsor also provided a copy of the portion of the label that contained the blinded treatment identity, the lot number and the expiration date, which match the descriptions in documents submitted to the Agency. In addition, the site stated that it would document and maintain such records for future bioequivalence studies. The site's response is adequate.

2. **Discrepancy between the case report form (CRF) and source document in the date of visit for Subject 482.**

The signature and sign-in log showed Subject 482 actually attended the clinic on 9/26/01 for Visit 3 whereas the CRF inaccurately showed the date of visit on 9/25/01. This transcription error should not have an impact on the study outcome.

3. **Failure to accurately document the final status for Subject 067 in the study exit form.**

This subject was discontinued from the study prematurely due to scheduled surgery on 8/15/01. In the study exit form dated 9/7/01, it was reported that this subject had completed the study. This transcription error would not affect the study outcome. The final study status of this subject was corrected in the CRF Exit Form on 9/28/01.

4. **Subject 076 was outside the 31-Day visit window (29-33 days).**

The site explained that Visit 1 on 8/13/01 was counted as Day 1. Therefore, the visit on 9/10/01 would be Day 29, which is within the window of 31 ± 2 stated in the protocol. Firm's response is acceptable.

5. **Failure to accurately report the number of subjects who prematurely terminated from the study in the Institutional Review Board (IRB) Termination Report.**

The IRB Termination report dated 01/18/02 showed only one patient (071) as an early termination. It did not show that patient 067 was also terminated from the study early due to back surgery. The firm has sent a letter to the IRB noting this omission from the final report. The site's corrective action is appropriate and acceptable.

1. **Lack of records to confirm batch/lot number of the test, reference and placebo drug products used in this study.**

Batch/lot numbers were not found in drug receipt records. The site has not responded to this 483 item. However, this issue has already been addressed above under _____. The site should be asked to document and maintain such records for future bioequivalence studies.

2. **Failure to retain reserve samples for shipments dated 8/15/01 (# 421-440) and 9/5/01 (# 581-600).**

This site received three shipments of study medication: a) Subject Nos. 101-120 on 7/18/01, b) Subject Nos. 421-440 on 8/15/01 and c) Subject Nos. 581-600 on 9/5/01. Reserve samples (# 101-105) were collected randomly from the initial shipment on 7/18/01 per the sponsor's instructions (sponsor's memo dated 7/2/01). These reserve samples were subsequently sent to _____. The site should comply with the Final Rule for retention of bioavailability (BA) and bioequivalence (BE) testing samples in their future studies, which requires that retention samples be collected from each shipment received by the clinical site. The site should also be informed that _____ dose not qualify as an independent third party storage facility, in that _____ was involved in labeling of the study medications and in developing the randomization schedule, with the coordination of _____.

1. **Failure to retain reserve samples for shipment dated 8/21/01 (# 561-580).**

This site received two shipments of study medication: a) Subject Nos. 121-140 on 7/12/01 and b) Subject Nos. 561-580 on 8/29/01. Reserve samples (# 136-140) were collected randomly from the shipment on 7/12/01 per sponsor's instruction (sponsor's memo dated 7/2/01). These reserve samples were sent to ——— for long-term storage, as the site did not have sufficient storage facility. The site responded to this issue in a letter dated 5/27/03, that they were asked by the sponsor to select reserve samples only from the initial shipment on 7/12/01. The site also acknowledged that it did not know that ——— was not an independent third party. The site should comply with the Final Rule for retention of BA and BE testing samples in their future studies, which requires that retention samples should be collected from each shipment received by the clinical site. The site should also be informed that ——— does not qualify as an independent third party storage facility.

2. **Protocol violation in that a) Subject 131 was 10 Days late for Visit 4, b) Subject 576 was 3 days late for Visit 4 and c) Subjects 571 and 580 were one day late for Visit 4 and Subject 579 was one day late for Visit 3.**

The firm responded to these protocol violations that these patients failed to show up at the scheduled visit date due to their personal problems (transport, etc.). The firm made every possible attempt (via telephone calls) to see the patients within the visit window. The firm's response is acceptable. However, the reviewer may decide whether these subjects should be excluded from data analysis.

3. **Visit 4 dermatological examination for patient 563 was conducted by the subinvestigator, ———, who was not a board certified dermatologist and who was also not the same examiner that conducted the Visit 1-3 exams for this subject.**

The protocol required that the investigator responsible for conducting dermatological assessments must be a board-

certified dermatologist and that the same investigator should evaluate subjects at each subsequent visit.

The subinvestigator, [redacted] evaluated the above patient on Visit 4 in the absence of the principal investigator. This has happened on only one occasion. This was appropriately documented in the source document. We are of the opinion that this protocol violation would not affect the study outcome. However, this type of protocol violation should be avoided in future studies.

Conclusions:

The Division of Scientific Investigation recommends that the study CPL-102 be accepted for review. It should be noted that the sites should comply with the Final Rule for retention of BA and BE testing samples in their future studies.

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

7/7/03

Tamal K. Chakraborti, Ph.D.

Final Classifications:

[redacted] - VAI

[redacted] - VAI

[redacted]

VAI

cc:

HFA-224
HFD-45/RF ACH
HFD-48/Chakraborti/Himaya/CF
HFD-600/Scardina
HFD-600/Kim
HFR-SW1540/Martinez
HFR-PA3540/Anderson
FACTS: 408075
Drafted: TKC 7/2/03
Edited: MKY 7/2/03
Edited: MFS 7/7/03 MFS
DSI:5465; O:\BE\eircover\76419cla.ket.doc

FILE COPY

MEMORANDUM

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

DATE: 3/24/03

TO: C.T. Viswanathan, Ph.D.
Associate Director, Division of Scientific Investigations
MPN I, HFD-48

THROUGH: Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence, HFD-650

FROM: DBE/GBIB Liaison
Division of Bioequivalence, Office of Generic Drugs, HFD-617, MPN II

SUBJECT: Biopharmaceutics Compliance Program 7348.001

Request for Inspection

References:

ANDA# 76-419
Product Ketoconazole Shampoo, 2%
Sponsor Clay-Park Labs, Inc. / Agis Group
(full address, phone, fax, contact) 1700 Bathgate Avenue
Bronx, NY 10457 Fax: 718-960-0111
Contact: Cardis Edwards Phone: 718-960-9976
Submission Date May 24, 2002

Priority C

A (highest) = ready for approval, outstanding issues
B = Bio review complete, pending chemistry
C (routine) = Bio under review

Due Date 6/24/03

APPEARS THIS WAY ON ORIGINAL

1. Studies

Study #1
Number: CPL-102
Title: Double-Blind, Randomized, Parallel-Group, Placebo Controlled, Multi-Center Study to Evaluate the Safety & BE of Clay-Park's Ketoconazole Shampoo and Nizoral® Shampoo in Subjects with Tinea Versicolor

Clinical Site (full address, phone, fax): [redacted]

Investigator/Contact

Analytical Site (full address, phone, fax): N/A

Investigator/Contact
Analytical Method

APPEARS THIS WAY ON ORIGINAL

Study #2
Number
Title: AS ABOVE

Clinical Site (full address, phone fax): [redacted]

Investigator/Contact

Analytical Site (full address, phone, fax): N/A

Investigator/Contact
Analytical Method

Study #3
Number
Title: AS ABOVE

Clinical Site (full address, phone, fax): [redacted]

Investigator/Contact

Analytical Site (full address, phone, fax)

APPEARS THIS WAY ON ORIGINAL

Investigator/Contact
Analytical Method

1. Reason for Inspection Request

_____ Not inspected in the last three years
_____ For Cause/Violative history
__X__ New Site
_____ Other

COMMENTS:

*The CRO is [redacted]

*There is a total of 25 individual sites used. Please see attached. We have chosen the 3 sites that enrolled the most patients.

2. Bio-study Status

__X__ Study under review
_____ Study review completed
  _____ study incomplete pending additional information from sponsor
  _____ study unacceptable with questionable data pending inspection verification
  _____ study acceptable pending satisfactory inspection results
_____ Other:

*Please let me know if you need additional information. The reviewer will forward her review for your information when it is complete.

CC:

HFD-617 (DBE/GBIB Liaison)
HFD-48 (Viswanathan)
HFD-600 (Bio Reviewer) Carol Kim
HFD-600 (PM) Krista Scardina
HFD-630 (ANDA# 76-419)

Scardina, Krista

From: Yau, Martin K
Sent: Monday, March 24, 2003 10:06 AM
To: Scardina, Krista
Cc: Chakraborti, Tamal K; Skelly, Michael F
Subject: RE: Site History

Krista:

DSIBE does not have site inspection history for the sites listed in your e-mail. However, [redacted] is scheduled to be inspected soon on April 13 for ANDA 76-294 (Ketoconazole Cream, 2%).

Martin

-----Original Message-----
From: Scardina, Krista
Sent: Monday, March 24, 2003 9:15 AM
To: CDER DSI Bioequivalence
Subject: Site History

Hello

I have a bioequivalence study with clinical endpoints that utilizes 25 centers. The CRO that manages the sites is [redacted] The three sites with the most patients are as follows:

[redacted]

Some of the other centers include:

[redacted]

Do we have a history on any of these sites?

Thanks for your input.

Krista

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-419

CORRESPONDENCE

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

December 29, 2003

Frank O. Holcombe, Jr., PhD
Associate Director for Chemistry
Food and Drug Administration
CDER, OGD
Document Control Room
Metro North II, HFD-600
7500 Standish Place, Room # 150
Rockville, MD 20855-2773

DRUG AMENDMENT
N/A

TELEPHONE AMENDMENT
SUBMITTED BY FAX
HARD COPY TO FOLLOW

Re: ANDA # 76-419, Ketoconazole Shampoo, 2%

Dear Dr. Holcombe:

Based on our telephone conversation with the Agency today, Clay-Park Labs, Inc. hereby provides the following information, as requested:

- **Table 1** provides the viscosity of the two production batches, Lot # VA 469 and Lot # VA 470, before and after the addition of sodium chloride stock solution (see **Attachment 1**).

- The following literature references, which demonstrate that sodium chloride (NaCl) is routinely used to increase the viscosity of shampoo formulations (see **Attachment 2**).

References:

1. Hunting, Anthony, L.L., "Encyclopedia of Shampoo Ingredients", p 214 – 215, Micelle Press: Cranford, NJ 1991.
2. McEwen, Gerald N., Ranae Canterbery Pepe and John A. Wenninger, "International Cosmetic Ingredient Dictionary and Handbook Vol. 2" p 1544, The Cosmetic, Toiletry, and Fragrance Association: Washington, D.C.
3. Moore, R.J., and J.B. Wilkinson, "Harry's Cosmeticology", p 446, Longman Scientific and Technical: Great Britain 1982.
4. Wade, Ainley and Paul J. Weller, "Handbook of Pharmaceutical Excipients", p 439, American Pharmaceutical Association: Washington 1994.

RECEIVED
DEC 30 2003
OGD/CDER

We hope that this information is adequate to allow us to obtain product approval.

Should you require any further information please contact the undersigned as follows:

Phone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Vice President of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

December 23, 2003

Frank O. Holcombe, Jr., PhD
Associate Director for Chemistry
Food and Drug Administration
CDER, OGD
Document Control Room
Metro North II, HFD-600
7500 Standish Place, Room # 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A

TELEPHONE AMENDMENT
SUBMITTED BY FAX
HARD COPY TO FOLLOW

Re: ANDA # 76-419, Ketoconazole Shampoo, 2%

Dear Dr. Holcombe:

In response to our telephone discussion on Monday, December 22, 2003, regarding the NaCl content in the bio-batch of Ketoconazole Shampoo, 2%, ANDA # 76-419, Clay-Park Labs, Inc. hereby provides the following scientific rationale.

[ ]

Upon review of the formulation and the executed batch records, we hereby state the following scientific rationale to demonstrate that the addition of NaCl to the product for the purpose of ——————— does not affect the cloud point, impact product stability, permeability or penetration characteristics of the drug product, Ketoconazole Shampoo, 2%. Additionally, it should be noted the innovator product also contains NaCl.

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A. The bio-batch, Lot # RX082, used to conduct the bioequivalence study contains NaCl.

1.

The specification for NaCl in is NMT The concentration of in the formulation is **(See page # 3201 of the Original ANDA)** and the content of NaCl in the lot of that was used to manufacture Lot # RX082 was **(See page # 2973 of the Original ANDA)**.

Quantity of NaCl in Lot # RX082:

$$\frac{\quad}{100} =$$

2.

concentration of HCl, NF in the formulation is **(See page # 3200 of the Original ANDA)**.

Quantity of HCl, NF in Lot # RX082:

$$\frac{\quad}{100} = \quad\% \text{ of HCl}$$

Quantity of NaCl in Lot # RX082:

$$\frac{\quad (\text{MW of NaCl})}{\quad (\text{MW of HCl})} =$$

3. **Total Quantity of NaCl in Bio Batch, Lot # RX082**:

B.

Table 1					
Description	**Lot #**	**Date Manufactured**	**Batch Size**	**Additional NaCl (As per Step # 33)**	
Bio-Batch	RX082	11/01/00		NA	
Nizoral® Shampoo, 2% (used in Bio Study)	OOKL683	N/A	N/A	NA	
Production Batch	VA 469	07/02/03			
Production Batch	VA 470	07/15/03			

N/A – Not Applicable
NA – Not Added

C. The formulation is not an emulsion. An emulsion is a two phase system in which one liquid is dispersed throughout another liquid in the form of small droplets as defined by USP 27 page # 2582. This product is a shampoo which consists of single phase system and therefore cannot be compared to an emulsion. The addition of NaCl, therefore cannot affect the "emulsion" characteristics as stated by the Agency.

D. A review of the innovator labeling **(See page # 0067 of the Original ANDA)** demonstrates that the innovator product contains NaCl as an inactive ingredient.

Further, as per our telephone conversation with the Agency today, we herby provide the Control Room Temperature stability data accrued to date, for the batches where sodium chloride was added to [redacted] **(See Attachment 1)**.

Additionally, we are also providing a stability testing commitment to place all production batches, which require addition of sodium chloride (NaCl) to [redacted], on stability at 25°C/ 60% RH (CRT) until such time that a specification range of "stock" NaCl solution to be used in the manufacturing process has been established (**See Attachment 2**).

Should you require any further information please contact the undersigned as follows:

Phone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Vice President of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

NEW CORRESP

NC

December 4, 2003

Mr. Gary Buehler, Director
Food and Drug Adminstration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Submitted by FAX – Hard Copy to Follow

PATENT AMENDMENT

RE: ANDA # 76-419 for Ketoconazole Shampoo, 2%

Dear Mr. Buehler:

Clay-Park Labs, Inc. herby submits a Patent Amendment to update the Patent Certification submitted on page 0014 of the original application for Ketoconazole Shampoo, 2%, ANDA #76-419 from Paragraph III to Paragraph II.

Enclosed is the updated statement of patent certification for Clay-Park Labs, Inc.'s Abbreviated New Drug Application for Ketoconazole Shampoo, 2%.

This statement is in accord with the Federal Food, Drug and Cosmetic Act, as amended September 24, 1984, and with the final regulations effective November 2, 1984.

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Should you have any comment or require any further clarifications on this amendment please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Vice President of Regulatory Affairs

Cc. Wanda Pamphile, Project Manager
Jerome Woyshner, Director (FDA District Office – Jamaica, NY)

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

May 6, 2003

ORIG AMENDMENT
W/IAIS

Krista Scardina, Pharm D., Project Manager
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-615
7500 Standish Place, Room 150
Rockville, MD 20855

TELEPHONE AMENDMENT

Re: ANDA #76-419 Ketoconazole Shampoo, 2%

Dear Ms. Scardina:

As per your fax correspondence, dated May 1, 2003 (see **Attachment A**), Clay-Park Labs, Inc. hereby provides the agency with the requested information, designated as a "Telephone Amendment". We trust that the clarification and/ or additional information provided herein satisfies your requirements in order to complete the review of the bioequivalence study with clinical endpoints for ANDA 76-419 for Clay-Park Labs, Inc.'s Ketoconazole Shampoo, 2%.

Should you require any further information, please do not hesitate to contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718)-960-0111**

Sincerely,

Candis Edwards
Vice President, Regulatory Affairs

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MAY 6 - 2003
OGD / CDER

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

March 6, 2003

Benjamin Lim, Chemistry Reviewer
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-615
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AM

Telephone Amendment
Submitted By Fax, Hard Copy To Follow

Re: ANDA #76-419 Ketoconazole Shampoo, 2%

Dear Mr. Lim:

As per our telephone conversation held on March 5, 2003, in response to your request, we have revised the specifications for Individual Related Substances in Ketoconazole Shampoo, 2% as follows:

Monograph	Specifications			
	Individual Related Substances		Total Related Substances	
	Old	New	Old	New
Bulk Product	NMT —	NMT —	NMT —	NMT —
Finished Product	NMT —	NMT —	NMT —	NMT —
Stability Product	NMT —	NMT —	NMT —	NMT —

Clay-Park Labs, Inc.'s revised bulk, finished and stability monographs are presented in **Attachment A**.

The revised specifications were based on the 1, 2, and 3 months, accelerated temperature stability data for the brand product Nizoral ®(ketoconazole) 2% Shampoo, Lot # 00FL804 (Expiration Date: June 2002).

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The following table summarizes the data obtained from the testing of the brand samples.

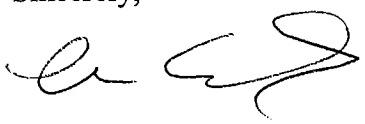
TEST	TEST INTERVAL			
Related Substances	Initial	1 Month	2 Months	3 Months
Individual	0.39	0.37, 0.37	0.34, 0.35	0.34, 0.35
Total	0.60	0.61, 0.61	0.66, 0.62	0.42, 0.46

We hope this will satisfy the agency's request.

Should you require further assistance, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,



Candis Edwards
Vice President of Regulatory Affairs
Clay-Park Labs, Inc.

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

FIELD COPY CERTIFICATION

This is to certify that the field copy (third copy) of the minor amendment to ANDA #76-419 for Ketoconazole Shampoo, 2% is a true copy of the original submission to the FDA. The field copy has been forwarded to the local New York District Office for their reference.

Candis Edwards
Vice President of Regulatory Affairs
Clay-Park Labs, Inc.

3/6/03

Date

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

March 6, 2003

Jerome Woyshner, District Director
Food and Drug Administration
New York District
158-15 Liberty Avenue
Jamaica, New York 11433

Telephone Amendment

Re: ANDA #76-419 Ketoconazole Shampoo

Dear Mr. Woyshner:

As required by 21 CFR 314.94 (d) (5), Clay-Park Labs, Inc. hereby forwards a true copy of the Telephone Amendment on our ANDA #76-419.

In response to our telephone conversation with Shing Hou Liu (Team Leader) and Benjamin Lim (Reviewing Chemist) on March 5, 2003, in reference to their request, we have revised the specifications for Individual Related Substances in Ketoconazole Shampoo as follows:

Monograph	Specifications			
	Individual Related Substances		Total Related Substances	
	Old	New	Old	New
Bulk Product	NMT [redacted]	NMT [redacted]	NMT [redacted]	NMT [redacted]
Finished Product	NMT [redacted]	NMT [redacted]	NMT [redacted]	NMT [redacted]
Stability Product	NMT [redacted]	NMT [redacted]	NMT [redacted]	NMT [redacted]

Clay-Park Labs, Inc.'s revised bulk, finished and stability monographs are presented in **Attachment A**.

The revised specifications were based on the 1, 2, and 3 months, accelerated temperature stability data for the brand product Nizoral ®(ketoconazole) 2% Shampoo, Lot # 00FL804 (Expiration Date: June 2002) as indicated below.

TEST	TEST INTERVAL			
Related Substances	Initial	1 Month	2 Months	3 Months
Individual	—	—	—	—
Total	—	—	—	—

We hope this will satisfy the agency's request.

Should you require further assistance, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Vice President of Regulatory Affairs
Clay-Park Labs, Inc.

APPEARS THIS WAY
ON ORIGINAL

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

January 6, 2003

Peter Rickman, Acting Director
Division of Labeling and Program Support
Food and Drug Administration Office of Generic Drugs, CDER
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
NIAF

LABELING AMENDMENT

Re: ANDA #76-419 Ketoconazole Shampoo, 2%

Dear Mr. Rickman:

In reference to the deficiency letter for the Labeling section dated December 9, 2002 **(Attachment A)** on our abbreviated new drug application for Ketoconazole Shampoo, 2% ANDA #76-419, Clay-Park Labs, Inc. hereby submits the deficiency response for the Labeling section, designated as Labeling Amendment.

Should you require any further assistance, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Director of Regulatory Affairs

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JAN 07 2003
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CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

ORIG AMENDMENT

January 6, 2003

N/A F

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

LABELING AMENDMENT

Re: ANDA #76-419 Ketoconazole Shampoo, 2%

Dear Sir or Madam:

We have enclosed the Labeling Amendment to Clay-Park Labs, Inc.'s ANDA # 76-419 for Ketoconazole Shampoo, 2% which contains the response to the labeling deficiency letter for the Labeling Section dated December 9, 2002.

Please note that there are three (3) binders enclosed: one **Archival Copy** , one **Review Copy** and additionally , a courtesy copy for Jim Barlow.

Should you have any questions, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Director of Regulatory Affairs

RECEIVED

JAN 07 2003

OGD / CDER

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

January 6, 2003

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

LABELING AMENDMENT

Re: ANDA #76-419 Ketoconazole Shampoo, 2%

Dear Mr. Barlow:

We are forwarding to you a copy of the Labeling Amendment to Clay-Park Labs, Inc.'s ANDA # 76-419 for Ketoconazole Shampoo, 2% which contains the response to the labeling deficiency letter for the Labeling Section dated December 9, 2002 (see **Attachment A**).

Should you require any further assistance, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Director of Regulatory Affairs

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

December 31, 2002

ORIG AMENDMENT
N/Am

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

MINOR AMENDMENT

Re: ANDA #76-419 for Ketoconazole Shampoo, 2%

Dear Ms. Pamphilc :

In reference to the deficiency letter for the Chemistry section dated November 15, 2002 **(Attachment A)** on our abbreviated new drug application for Ketoconazole Shampoo, 2%, ANDA #76-419 Clay-Park Labs, Inc. hereby submits the deficiency response for the Chemistry section, designated as a Minor Amendment.

Should you require any further assistance, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,

Candis Edwards
Director of Regulatory Affairs

RECEIVED
JAN 0 6 2003
OGD / CDER

ANDA 76-419

Clay-Park Labs, Inc.
Attention: Candis Edwards
1700 Bathgate Avenue
Bronx, NY 10457

JUL 15 2002

Dear Madam:

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

Reference is made to the telephone conversation dated July 11, 2002 and to your correspondence dated July 11, 2002.

NAME OF DRUG: Ketoconazole Shampoo, 2%

DATE OF APPLICATION: May 24, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: May 28, 2002

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

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

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

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

CLAY-PARK LABS, INC.

AGIS GROUP

1700 BATHGATE AVE. BRONX, NY 10457 (718)901-2800

May 24, 2002

505(j)(2)(A) OK
15-JUL-2002
Gregory S. Davis

Mr. Gary Buehler, Director
Food and Drug Administration
Office of Generic Drugs, CDER
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA for Ketoconazole Shampoo, 2%

Dear Mr. Buehler,

Clay-Park Labs, Inc. hereby submits an original abbreviated new drug application (ANDA) in hard copy format to seek approval to market Ketoconazole Shampoo, 2% that is bioequivalent to the reference listed drug NIZORAL® (ketoconazole) 2%, distributed by JANSSEN PHARMACEUTICA INC. to NDA # 019927.

This ANDA consists of eight (8) volumes. Clay-Park Labs, Inc. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and a technical review copy (in red folders) that contains all the information in the archival copy with the exception of the bioequivalence section (VI). A separate copy of the bioequivalence section is provided in orange folders.

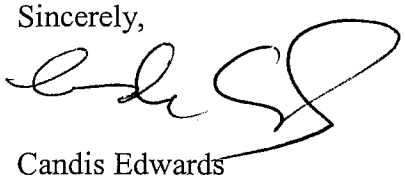
This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) is being sent to our local district office. This "field copy" is contained in burgundy folders.

For more detailed information on the organization of this ANDA, please refer to the "Executive Summary" attached after the Table of Contents.

Should you have any comments or require any further clarification on this ANDA, please contact the undersigned as follows:

Telephone: (718) 960-9976 **Fax: (718) 960-0111**

Sincerely,



Candis Edwards
Director of Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL