CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-574

Name: Econazole Nitrate Cream, 1%

Sponsor: Healthpoint, Ltd.

Approval Date: December 17, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-574

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Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-574

APPROVAL LETTER

ANDA 76-574

DEC 17 2004

Healthpoint, Ltd.
Attention: Bobbi S. Woodward
3909 Hulen Street
Fort Worth, TX 76107

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 16, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Econazole Nitrate Cream, 1%.

Reference is also made to your amendments dated December 19, 2003, and February 26, May 1, and November 12, 2004.

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 Econazole Nitrate Cream, 1%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Spectazole® Cream, 1%, of Johnson and Johnson Consumer Companies, Inc.).

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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in

draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Robert Lee Sest/for
12/17/2004

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-574

LABELING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

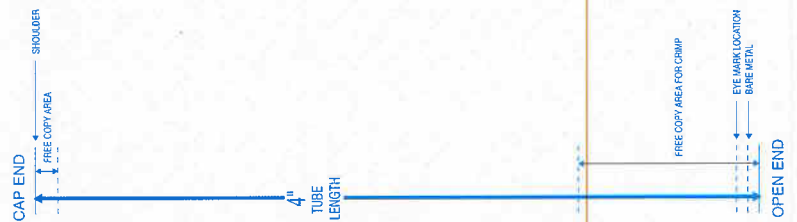
ANDA 76-574

LABELING REVIEWS

Blue PMS 312
Black
Do not print Die line (Process Blue)

3/4" 15g die line

Blue PMS 312
Black
Do not print Die line (Process Blue)



FOR TOPICAL USE ONLY – NOT FOR OPHTHALMIC USE.
WARNING: KEEP OUT OF REACH OF CHILDREN

USUAL DOSAGE: See package insert for complete prescribing information.
Contains econazole nitrate1% in water miscible base of pegoxol 7 stearate, peglicol 5 oleate, mineral oil, benzoic acid, butylated hydroxyanisole, and purified water.

Store at controlled room temperature 20°-25°C (68°-77°F).

See crimp for lot no. and expiration date.

IMPORTANT: Do not use if seal has been punctured or is not visible.

TO OPEN: Use cap to puncture seal.

REORDER NO. 0064-5000-15 102353-1003

Marketed by:
HEALTHPOINT®
Healthpoint, Ltd.
Fort Worth, Texas 76107
1-800-441-8227 www.healthpoint.com
Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215

NDC 0064-5000-15

APPROVED DEC 17 2004

Econazole Nitrate Cream 1%

Rx ONLY NET WT 15 g

HEALTHPOINT

Blue PMS 312
Black
Do not print Die line (Process Blue)

7/8 - 30G die line

FOR TOPICAL USE ONLY – NOT FOR OPHTHALMIC USE.
WARNING: KEEP OUT OF REACH OF CHILDREN

USUAL DOSAGE: See package insert for complete prescribing information.
Contains econazole nitrate1% in a water miscible base of pegoxol 7 stearate, peglicol 5 oleate, mineral oil, benzoic acid, butylated hydroxyanisole, and purified water.

Store at controlled room temperature 20°-25°C (68°-77°F).

See crimp for lot no. and expiration date.

IMPORTANT: Do not use if seal has been punctured or is not visible.

TO OPEN: Use cap to puncture seal.

REORDER NO. 0064-5000-30 / 102354-1003

NDC 0064-5000-30

APPROVED DEC 17 2004

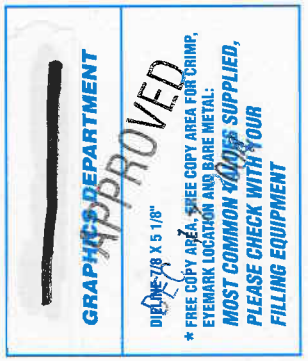
Marketed by:
HEALTHPOINT®
Healthpoint, Ltd.
Fort Worth, Texas 76107
1-800-441-8227
www.healthpoint.com

Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215

Econazole Nitrate Cream 1%

Rx ONLY NET WT 30 g

HEALTHPOINT



Blue PMS 312
Black
Do not print Die line (PMS 291)

FOR TOPICAL USE ONLY – NOT FOR OPHTHALMIC USE.
WARNING: KEEP OUT OF REACH OF CHILDREN

USUAL DOSAGE: See package insert for complete prescribing information.
Contains econazole nitrate1% in a water miscible base of pegoxol 7 stearate, peglicol 5 oleate, mineral oil, benzoic acid, butylated hydroxyanisole, and purified water.

Store at controlled room temperature 20°-25°C (68°-77°F).

See crimp for lot no. and expiration date.

IMPORTANT: Do not use if seal has been punctured or is not visible.

TO OPEN: Use cap to puncture seal.

REORDER NO. 0064-5000-85 102355-1003

APPROVED
DEC 17 2001

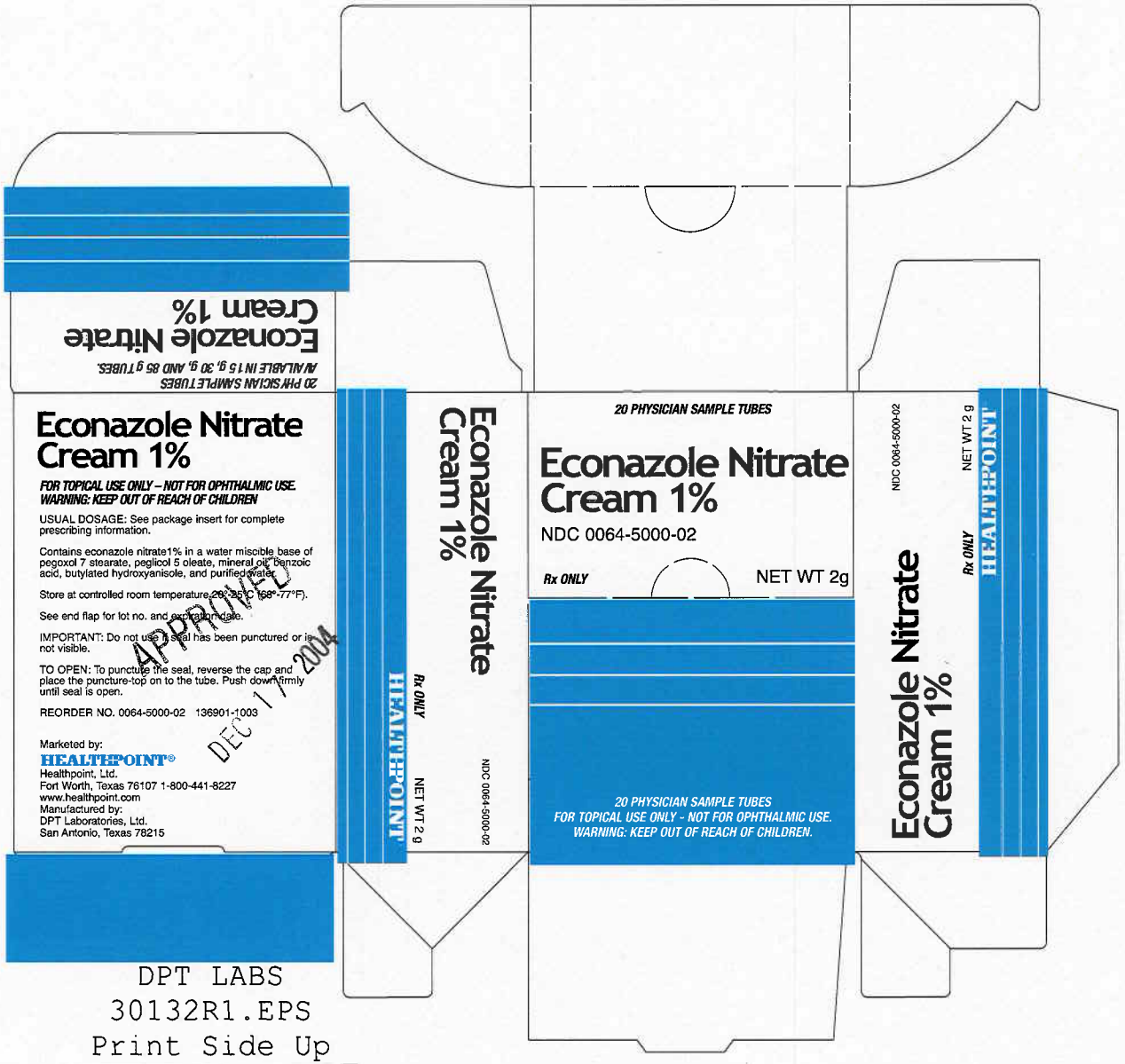
Marketed by:
HEALTHPOINT®
Healthpoint, Ltd.
Fort Worth, Texas 76107 1-800-441-8227 www.healthpoint.com
Manufactured by:
DPT Laboratories, Ltd. San Antonio, Texas 78215

NDC 0064-5000-85

Econazole Nitrate Cream 1%

Rx ONLY NET WT 85 g

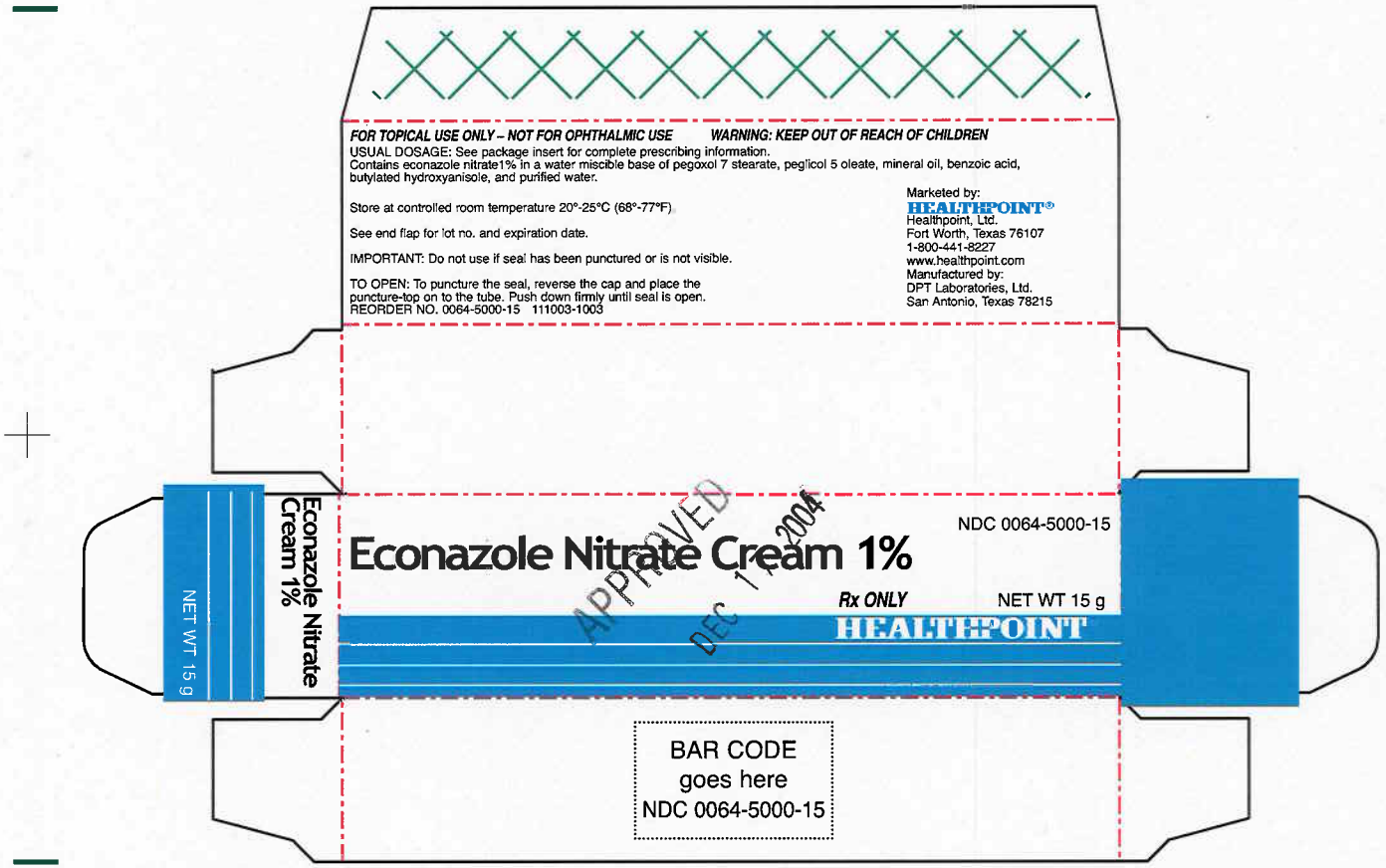
HEALTHPOINT



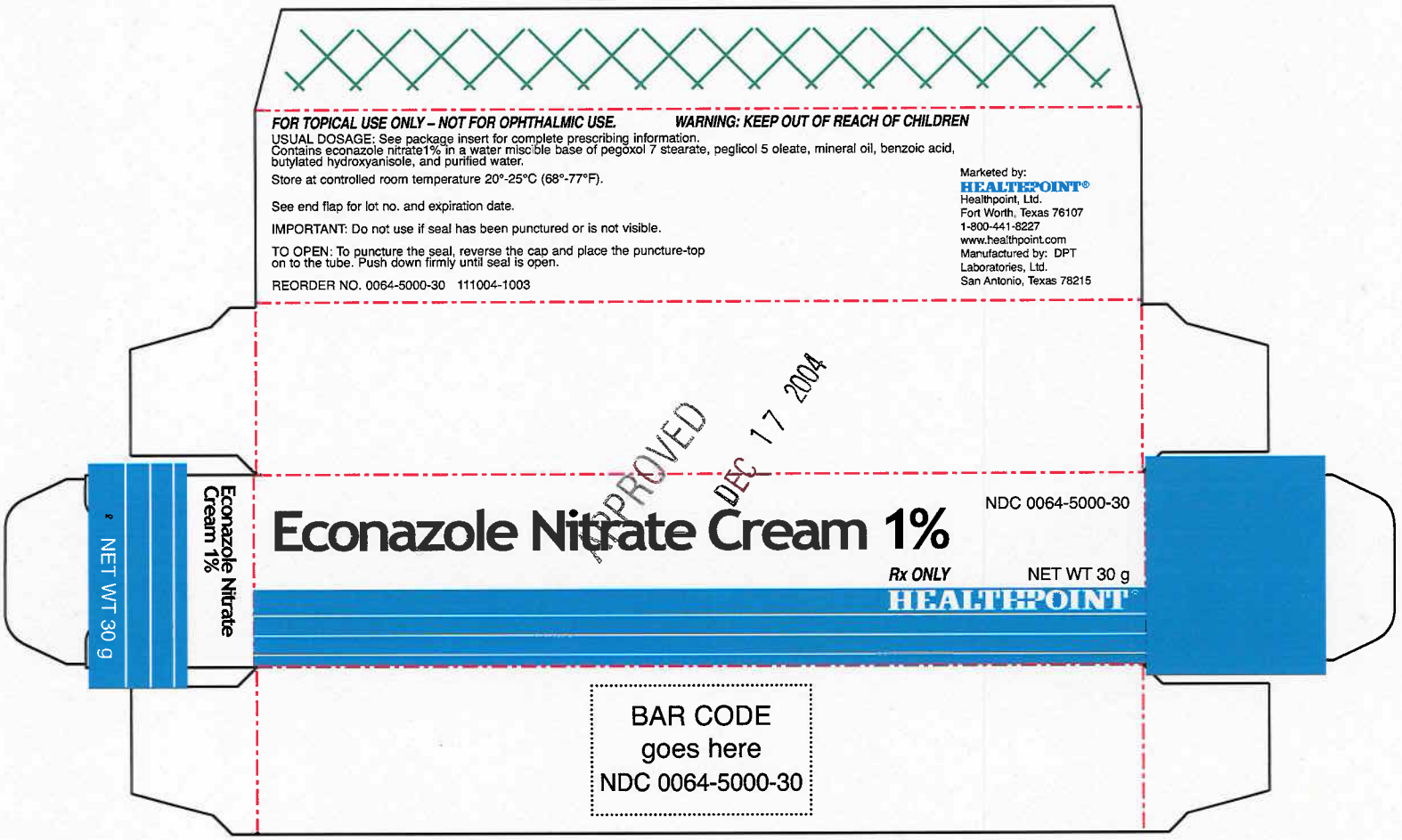
DPT LABS
30132R1.EPS
Print Side Up

05-Sep-2002

Blue PMS 312
Black
Do not print Die line



Blue PMS 312
Black
Do not print Die line (Process Blue)



Blue PMS 312
Black
Do not print Die line

FOR TOPICAL USE ONLY – NOT FOR OPHTHALMIC USE.
WARNING: KEEP OUT OF REACH OF CHILDREN

USUAL DOSAGE: See package insert for complete prescribing information.
Contains econazole nitrate1% in a water miscible base of pegoxol 7 stearate, peglicol 5 oleate, mineral oil, benzoic acid, butylated hydroxyanisole, and purified water.

Store at controlled room temperature 20°-25°C (68°-77°F).

See end flap for lot no. and expiration date.

IMPORTANT: Do not use if seal has been punctured or is not visible.

TO OPEN: To puncture the seal, reverse the cap and place the puncture-top on to the tube. Push down firmly until seal is open.

REORDER NO. 0064-5000-85 111005 -1003

Marketed by:
HEALTHPOINT®
Healthpoint, Ltd.
Fort Worth, Texas 76107 1-800-441-8227 www.healthpoint.com
Manufactured by: DPT Laboratories, Ltd. San Antonio, Texas 78215

APPROVED DEC 17 2004

NET WT 85 g

Econazole Nitrate Cream 1%

Econazole Nitrate Cream 1%

NDC 0064-5000-85

Rx ONLY

NET WT 85 g

HEALTHPOINT®

BAR CODE
goes here
NDC 0064-5000-85

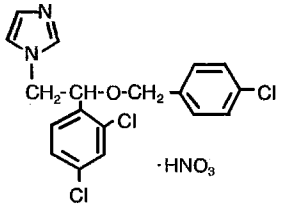
Econazole Nitrate Cream 1%

Prescribing Information

DESCRIPTION:

Econazole Nitrate Cream 1% contains the antifungal agent, econazole nitrate 1% in a water miscible base consisting of pegoxol 7 stearate, peglicol 5 oleate, mineral oil, benzoic acid, butylated hydroxyanisole, and purified water. The white to off-white soft cream is for topical use only.

Chemically, econazole nitrate is 1-[2-{(4-chloro-phenyl) methoxy}-2-(2,4- dichlorophenyl)ethyl]-1H-imidazole mononitrate. Its structure is as follows:



CLINICAL PHARMACOLOGY:

After topical application to the skin of normal subjects, systemic absorption of econazole nitrate is extremely low. Although most of the applied drug remains on the skin surface, drug concentrations were found in the stratum corneum which, by far, exceeded the minimum inhibitory concentration for dermatophytes. Inhibitory concentrations were achieved in the epidermis and as deep as the middle region of the dermis. Less than 1% of the applied dose was recovered in the urine and feces.

Microbiology: Econazole nitrate has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

FOR TOPICAL DERMATOLOGIC USE ONLY – NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

Dermatophytes	**Yeasts**
Epidermophyton floccosum	*Candida albicans*
Microsporum audouini	*Malassezia furfur*
Microsporum canis	
Microsporum gypseum	
Trichophyton mentagrophytes	
Trichophyton rubrum	
Trichophyton tonsurans	

Econazole nitrate exhibits broad-spectrum antifungal activity against the following organisms ***in vitro*, <u>but the clinical significance of these data is unknown.</u>**

Dermatophytes	**Yeasts**
Trichophyton verrucosum	*Candida guillermondii*
	Candida parapsilosis
	Candida tropicalis

INDICATIONS AND USAGE:

ECONAZOLE NITRATE CREAM 1% is indicated for topical application in the treatment of tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Microsporum canis, Microsporum audouini, Microsporum gypseum,* and *Epidermophyton floccosum,* in the treatment of cutaneous candidiasis, and in the treatment of tinea versicolor.

CONTRAINDICATIONS:

ECONAZOLE NITRATE CREAM 1% is contraindicated in individuals who have shown hypersensitivity to any of its ingredients.

WARNINGS:

ECONAZOLE NITRATE CREAM 1% is not for ophthalmic use.

PRECAUTIONS:

General: If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.
For external use only. Avoid introduction of ECONAZOLE NITRATE CREAM 1% into the eyes.

Carcinogenicity Studies: Long-term animal studies to determine carcinogenic potential have not been performed.

Fertility (Reproduction): Oral administration of econazole nitrate in rats has been reported to produce prolonged gestation. Intravaginal administration in humans has not shown prolonged gestation or other adverse reproductive effects attributable to econazole nitrate therapy.

Pregnancy: Pregnancy Category C. Econazole nitrate has not been shown to be teratogenic when administered orally to mice, rabbits or rats. Fetotoxic or embryotoxic effects were observed in Segment I oral studies with rats receiving 10 to 40 times the human dermal dose. Similar effects were observed in Segment II or Segment III studies with mice, rabbits and/or rats receiving oral doses 80 or 40 times the human dermal dose. Econazole nitrate should be used in the first trimester of pregnancy only when the physician considers it essential to the welfare of the patient. The drug should be used during the second and third trimesters of pregnancy only if clearly needed.

Nursing Mothers: It is not known whether econazole nitrate is excreted in human milk. Following oral administration of econazole nitrate to lactating rats, econazole and/or metabolites were excreted in milk and were found in nursing pups. Also, in lactating rats receiving large oral doses (40 or 80 times the human dermal dose), there was a reduction in post partum viability of pups and survival to weaning; however, at these high doses, maternal toxicity was present and may have been a contributing factor. Caution should be exercised when econazole nitrate is administered to a nursing woman.

ADVERSE REACTIONS:

During clinical trials, approximately 3% of patients treated with econazole nitrate 1% cream reported side effects thought possibly to be due to the drug, consisting mainly of burning, itching, stinging, and erythema. One case of pruritic rash has also been reported.

OVERDOSE:

Overdosage of econazole nitrate in humans has not been reported to date. In mice, rats, guinea pigs and dogs, the oral LD_{50} values were found to be 462, 668, 272, and >160 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:

Sufficient ECONAZOLE NITRATE CREAM 1% should be applied to cover affected areas once daily in patients with tinea pedis, tinea cruris, tinea corporis, and tinea versicolor, and twice daily (morning and evening) in patients with cutaneous candidiasis. Early relief of symptoms is experienced by the majority of patients and clinical improvement may be seen fairly soon after treatment is begun; however, candidal infections and tinea cruris and corporis should be treated for two weeks and tinea pedis for one month in order to reduce the possibility of recurrence. If a patient shows no clinical improvement after the treatment period, the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment.

HOW SUPPLIED:

ECONAZOLE NITRATE CREAM 1% is supplied in tubes of 15 grams (NDC 0064-5000-15), 30 grams (NDC 0064-5000-30), and 85 grams (NDC 0064-5000-85).

Store at controlled room temperature 20°-25°C (68°-77°F).

Rx only.

Marketed by:
HEALTHPOINT®
Healthpoint, Ltd.
Fort Worth, Texas 76107
1-800-441-8227
www.healthpoint.com

Manufactured by:
DPT Laboratories, Ltd.
San Antonio, Texas 78215

127919-1003

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

ANDA Number: 76-574

Date of Submission: December 16, 2002

Applicant's Name: Healthpoint

Established Name: Econazole Nitrate Cream, 1%

Labeling Deficiencies:

1. **GENERAL COMMENT**

   Proprietary Name: We find your proposed proprietary name "[redacted] IS NOT acceptable. [redacted]

   APPEARS THIS WAY ON ORIGINAL

2. **CONTAINER:**

   15 g, 30 g, and 85 g

   i. Because your stability studies will be conducted at 25 ± 2°C, 60% ± 5% RH, revise your storage temperature to read "Store at 20 - 25°C (68 - 77°F) [see USP Controlled Room Temperature]".

   ii. We recommended revising the "Contains econazole nitrate... " sentence to read "Contains econazole nitrate 1% in a water-miscible base of pegoxol 7 sterate, peglicol 5 oleate, mineral oil ..... and purified water.

   iii. Increase the prominence of the established name to be in accordance with CRF 201.10 (2).

   2 g (physician sample)

   iv. See Container comments (i), (ii) and (iii)

   v. Your container label is difficult to read. Revise your container label to increase readability and delete the text that is obstructing the information on the label.

3. **CARTON:**

   2 g, 15 g, 30 g, 85 g tubes

   See (i), (ii) and (iii) under CONTAINER comments.

4. **INSERT:**

   See (i) and (iii) under CONTAINER comments.

Please revise your labels and labeling, as instructed above, and then submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug. In order to keep your ANDA 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/cdernew/listserv.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.

John D Grace for/

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

NOTES/QUESTIONS TO THE CHEMIST: None

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 24		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?			
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?	Name NOT acceptable		
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.		X	
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?		X	
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.		X	

FOR THE RECORD:

1. **MODEL LABELING**
   Review based on the labeling of the reference listed drug, Spectazole Cream, (NDA 18-751/S-011): Revised March 1994; Approved February 24, 1995).

2. **INACTIVE INGREDIENTS**
   There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.
   [Vol. A1.4 page 1703]

3. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   - USP: None
   - RLD: Store below 86°F
   - ANDA: Store at _____

Asked the firm to revise their storage temperature to read "Store at 20 - 25°C (68 - 77°F) [see USP Controlled Room Temperature]", because their stability studies are conducted at 25 ± 2°C, 60% ± 5% RH.

4. DISPENSING STATEMENT COMPARISON

- USP: None.
- RLD: None.
- ANDA: None.

5. PACKAGE CONFIGURATION

- RLD: Packaged in 15 g, 30 g, and 85 g tubes.
- ANDA: Packaged in 2 g tube (physician sample), 15 g, 30 g, and 85 g tubes.

6. CONTAINER/CLOSURE

The proposed drug product will be packaged in 2 g (sample), 15 g, 30 g, and 85 g blind-end lined aluminum tubes fitted with white polypropylene caps.
[Vol 1.5 Page 1901]

7. FINISHED DOSAGE FORM

- RLD: Supplied as 15 g, 30 g, and 85 g tubes.
- ANDA: Supplied as a white to off-white cream in 15 g, 30 g and 85 g aluminum tubes..

8. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

DPT Laboratories, Ltd.
San Antonia, Texas 78215

Date of Review: **Date of Submission: December 16, 2002**

Primary Reviewer: B. Weitzman **Date:** 5/29/03

B Weitzman

Team Leader: **Date:** 6/5/2003

cc: ANDA 76-574
DUP/DIVISION FILE
HFD-613/Bweitzman/JGrace (no cc)
V:\FIRMSAM\HealthPoint\LTRS&REV\76574na1.I
Review

APPROVAL SUMMARY

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

ANDA Number: 76-574 Date of Submission: **November 12, 2004**

Applicant's Name: Healthpoint

Established Name: Econazole Nitrate Cream, 1%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? Yes

1. **CONTAINER [2 g tube – professional sample]** – Satisfactory in FPL as of **November 12, 2004** paper submission. [code # 136902-1003]
2. **CONTAINER [15 g tube]** – Satisfactory in FPL as of **November 12, 2004** paper submission. [code # 102353-1003]
3. **CONTAINER [30 g tube]** – Satisfactory in FPL as of **November, 2004** paper submission. [code # 102354-1003]
4. **CONTAINER [85 g tube]** – Satisfactory in FPL as of **November 12, 2004** paper submission. [code # 102355-1003]
5. **CARTON [2 g tube – professional sample]** – Satisfactory in FPL as of **November 12, 2004** paper submission. [code # 136901-1003]
6. **CARTON [15 g tube]** – Satisfactory in FPL as of **November 12, 2004** paper submission. [code # 111003-1003]
7. **CARTON [30 g tube]** – Satisfactory in FPL as of **November 12, 2004** paper submission. [code # 111004-1003]
8. **CARTON [85 g tube]** – Satisfactory in FPL as of **November 12, 2004** paper submission. [code # 111005-1003]
9. **PACKAGE INSERT** - Satisfactory in FPL as of **November 12, 2004** paper submission. [code # 127919-0504]

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Spectazole Cream
- NDA Number: 18-751/S-011
- NDA Drug Name: Econazole Nitrate Cream, 1%
- NDA Firm: Johnson and Johnson
- Date of Approval of NDA Insert: February 24, 1995
- 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
- Basis of Approval for the Carton Labels: Side-by-side comparison
- Revisions needed post-approval: **YES**
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 18-751

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There are no unexpired patents for this product in the orange book database		N ONE

Exclusivity Data– NDA 18-751

Code	Reference	Expiration	Labeling Impact
	There are no unexpired exclusivity for this product		NONE

POST- APPROVAL REVISIONS - At the next printing make the following changes. You made submit the revisions in an annual report provided the changes are described in full. We refer you to 21 CRF 314.81 (b) (iii) for guidance.

GENERAL COMMENT [ALL LABELING] – Revise your storage temperature to read "Store at 20 - 25°C (68 - 77°F) [see USP Controlled Room Temperature]" rather than "Store at controlled room temperature 20 - 25°C (68 - 77°F)"

NOTES/QUESTIONS TO THE CHEMIST: None

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 24		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?	Name Unacceptable		
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
		X	

Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)			
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.		X	
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?		X	
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.		X	

FOR THE RECORD:

1. **MODEL LABELING**

   Review based on the labeling of the reference listed drug, Spectazole Cream, (NDA 18-751/S-011): Revised March 1994; Approved February 24, 1995).

   Please note that the firm proposed a proprietary name ——— The Division of Medication Errors and Technical Support **does <u>not</u> recommend** use of the proprietary name ———

2. **INACTIVE INGREDIENTS**
There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.
[Vol. A1.4 page 1703]

3. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
- USP: None
- RLD: Store below 86°F
- ANDA: Store at controlled room temperature 20 - 25°C (68 - 77°F)

4. **DISPENSING STATEMENT COMPARISON**
- USP: None.
- RLD: None.
- ANDA: None.

5. **PACKAGE CONFIGURATION**
- RLD: Packaged in 15 g, 30 g, and 85 g tubes.
- ANDA: Packaged in 2 g tube (physician sample), 15 g, 30 g, and 85 g tubes.

6. **CONTAINER/CLOSURE**
The proposed drug product will be packaged in 2 g (sample), 15 g, 30 g, and 85 g blind-end lined aluminum tubes fitted with white polypropylene caps.
[Vol 1.5 Page 1901]

7. **FINISHED DOSAGE FORM**
- RLD: Supplied as 15 g, 30 g, and 85 g tubes.
- ANDA: Supplied as a white to off-white cream in 15 g, 30 g and 85 g aluminum tubes..

8. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**
DPT Laboratories, Ltd.
San Antonia, Texas 78215

Date of Review: **Date of Submission: November 12, 2004**

Primary Reviewer: B. Weitzman **Date:** 12/01/2004

B. Weitzman

Team Leader: **Date:** 12/1/2004

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cc: ANDA 76-574
DUP/DIVISION FILE
HFD-613/Bweitzman/JGrace (no cc)
V:\FIRMSAM\HealthPoint\LTRS&REV\76574AP.I
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-574

CHEMISTRY REVIEWS

ANDA 76-574

Econazole Nitrate Cream, 1%

Healthpoint, Ltd.

Bing Cai, Ph.D.
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-574

2. REVIEW #: 1

3. REVIEW DATE: March 31, 2003

4. REVIEWER: Bing Cai

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original	16-December-2002
NC	16-January-2002
FDA Acknowledgment Letter (Acceptable for filing, 12-17-02)	17-January-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-December-2002
NC	16-January-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Healthpoint, Ltd.
Address:	318 McCullough, San Antonio, TX 78215
Representative:	Kay Mary Harrell
Telephone/Fax:	210-476-8184/210-227-6132

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ———
b) Non-Proprietary Name (USAN): Econazole Nitrate Cream, 1%

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug:	Spectazole® (econazole nitrate) Cream 1%
Holder:	Ortho Dermatological, Division of Ortho-McNeil Pharmaceutical, Inc. (Johnson & Johnson)
Application Number:	N018751
Strength:	1%
Patent Certification:	Paragraph II Certification (no unexpired patent)
Exclusivity:	None

10. PHARMACOL. CATEGORY: Antifungal agent

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

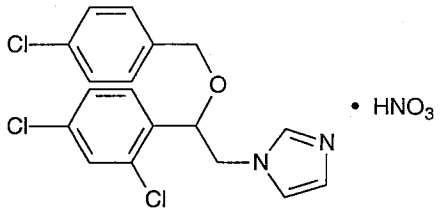
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

1*H*-Imidazole, 1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-, mononitrate, (±)-. $C_{18}H_{15}Cl_3N_2O \cdot HNO_3$ Mol.wt. 444.7 CAS No. 68797-31-9



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	adequate	10/30/02	By N. Nashed
	III			4			
	IV			4			
	IV			4			

[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: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Pending		
Labeling	Pending		
Bioequivalence	Pending		
EA	Waiver		
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 76-574

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval (minor amendment).

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

N/A

II. Summary of Chemistry Assessments

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

The reference listed drug for this application is Spectazole® (econazole nitrate 1%) Cream by Ortho Dermatological Division of Ortho-McNeil Pharmaceutical, Inc. (Johnson & Johnson).

The drug substance is Econazole Nitrate, USP and conforms to the USP monograph. The drug substance is a white or almost white crystalline powder and is known to exist in only one polymorphic form. Additional controls regarding the drug substance have been requested.

The drug product is Econazole Nitrate Cream, 1% and is for topical application in the treatment of tinea pedis, tinea cruris, and tinea corporis. The drug product contains as excipients; Pegoxyl-7 Stearate, Mineral Oil, Peglicol 5 Oleate, Butylated Hydroxyanisole, Benzoic Acid and Purified Water.

The drug product is manufactured by [redacted] and also provided specifications for release and stability.

The bulk drug product is packaged in 2 g (sample), 15 g, 30 g and 85 g blind-end [redacted] lined aluminum tubes fitted with white polypropylene caps. The firm has requested [redacted], which is not acceptable. The firm has provided satisfactory temperature cycling study results for the drug product.

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

N/A

C. Basis for Approvability or Not-Approval Recommendation

CMC deficiencies are related to the specifications for the drug substance, finished product and stability with related method validations.

Labeling and bioequivalence are pending.

III. Administrative

A. Reviewer's Signature

Bing Cai, Ph.D.

B. Endorsement Block

Chemist, B. Cai, Ph.D./HFD-620/ 8/15/05 revised
Chemistry Team Leader, S. Liu, Ph.D/HFD-620
Project Manager, W. Pamphile, PharmD/HFD-617/

C. CC Block

ANDA #76-574
ANDA #76-574/Division File
Field Copy

Redacted 24 page(s)

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information from

CHEMISTRY REVIEW #1

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

1. The bioequivalence and labeling sections of your application is under review and you will be notified separately of any deficiencies.

2. Since the drug product is not listed in the USP, the analytical methods must be validated by an FDA field laboratory. Samples for the methods validation will be requested by the FDA at the appropriate time upon the resolution of the method validation deficiencies indicated above. Please provide a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion.

3. The USP method for the drug substance is the regulatory method and will prevail in the event of a dispute.

4. A satisfactory compliance evaluation for each of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval.

APPEARS THIS WAY
ON ORIGINAL

5. Please provide any additional long term stability data that may be available.

Sincerely yours,

Paul Schwartz 5/12/09

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

cc: ANDA 76-574
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620 /BCai/03/31/03/04/15/03 4/29/03

HFD-620/SLiu, Team Leader/4/15/03 S.H. Liu 4/28/03

HFD-617/Wpamphile/4/25/03 5/8/03

F/T by :ard/4/28/03

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TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 76-574

Econazole Nitrate Cream, 1%

Healthpoint, Ltd.

Bing Cai, Ph.D.
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-574

2. REVIEW #: 2

3. REVIEW DATE: September 30, 2003

4. REVIEWER: Bing Cai

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Firm	
Original Submission	16-December-2002
NC	16-January-2003
FDA	
Acknowledgment Letter (Acceptable for filing, 12-17-03)	17-January-2003
NA letter, CMC	13-May-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC)	5-September-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Healthpoint, Ltd.
Address:	318 McCullough, San Antonio, TX 78215
Representative:	Mark A. Mitchell
Telephone/Fax:	210-476-8184/210-227-6132

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ———
b) Non-Proprietary Name (USAN): Econazole Nitrate Cream, 1%

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug:	Spectazole® (econazole nitrate) Cream 1%
Holder:	Ortho Dermatological, Division of Ortho-McNeil Pharmaceutical, Inc. (Johnson & Johnson)
Application Number:	N 18-751
Strength:	1%
Patent Certification:	Paragraph II Certification (no unexpired patent)
Exclusivity:	None

10. PHARMACOL. CATEGORY: Antifungal agent

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

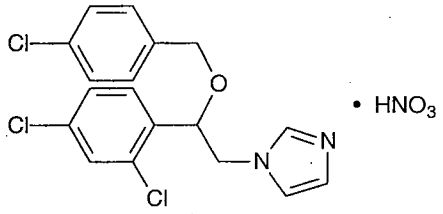
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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

1*H*-Imidazole, 1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-, mononitrate, (±)-. $C_{18}H_{15}Cl_3N_2O \cdot HNO_3$ Mol.wt. 444.7 CAS No. 68797-31-9



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	adequate	09/30/03	By B. Cai
	III			4			
	IV			4			
	IV			4			

[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: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	4/28/03	J. D'Ambrogio
Methods Validation	Will not be issued based on the current OGD guideline		
Labeling	Deficient	6/9/03	B. Weitzman
Bioequivalence	Pending		
EA	Waiver		
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 76-574

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval (minor amendment).

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

N/A

II. Summary of Chemistry Assessments

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

The reference listed drug for this application is Spectazole® (econazole nitrate 1%) Cream by Ortho Dermatological Division of Ortho-McNeil Pharmaceutical, Inc. (Johnson & Johnson).

The drug substance is Econazole Nitrate, USP and conforms to the USP monograph. The drug substance is a white or almost white crystalline powder and is known to exist in only one polymorphic form. Additional controls regarding the drug substance have been requested.

The drug product is Econazole Nitrate Cream, 1% and is for topical application in the treatment of tinea pedis, tinea cruris, and tinea corporis. The drug product contains as excipients; Pegoxyl-7 Stearate, Mineral Oil, Peglicol 5 Oleate, Butylated Hydroxyanisole, Benzoic Acid and Purified Water.

The drug product is manufactured by [ ] and also provided specifications for release and stability.

The bulk drug product is packaged in 2 g (sample), 15 g, 30 g and 85 g blind-end — lined aluminum tubes fitted with white polypropylene caps. The firm has requested a 24 month expiration date. The firm has provided satisfactory temperature cycling study results for the drug product.

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

N/A

C. Basis for Approvability or Not-Approval Recommendation

CMC deficiencies are related to manufacturing controls, finished product, and stability specifications and controls.

Labeling deficient
Bioequivalence pending

III. Administrative

A. Reviewer's Signature

Bing Cai, Ph.D.

B. Endorsement Block

Chemist, B. Cai, Ph.D./HFD-620/ 11/20/03
Chemistry Team Leader, S. Liu, Ph.D/HFD-620 for RSpandau 11/19/03
Project Manager, W. Pamphile, PharmD/HFD-617/

C. CC Block

ANDA #76-574
ANDA #76-574/Division File
Field Copy

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information from

CHEMISTRY REVIEW #2

cc: ANDA 76-574
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620 /Bcai, Ph.D./09/31/03

HFD-620/SLiu, Team Leader/ for RSpandau. 11/19/03

HFD-617/Wpamphile, PM/ 11/26/03

F/T by :

V:\FIRMSAM\HEALTHPO\LTRS&REV\76574cr2.bbc.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

ANDA 76-574

Econazole Nitrate Cream, 1%

Healthpoint, Ltd.

Bing Cai, Ph.D.
Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-574

2. REVIEW #: 3

3. REVIEW DATE: January 29, 2004 (Revised on 12/7/04)

4. REVIEWER: Bing Cai

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Firm	
Original Submission	16-December-2002
Amendment (CMC)	5-September-2003
FDA	
Acknowledgment Letter (Acceptable for filing, 12-17-03)	17-January-2003
NA letter, CMC	13-May-2003
Labeling def. letter	05-June-2003
NA letter, CMC	01-Dec-2003
T-con	26-Feb-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC)	19-Dec-2003
Amendment (Telephone, part A)	26-Feb-2004
Amendment (Telephone, part B)	26-Feb-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Healthpoint, Ltd.
Address:	318 McCullough, San Antonio, TX 78215
Representative:	Bobbi Woodward // Dina Mckinney
Telephone/Fax:	817-916-2307/817-~~900-4107~~ 916-2800

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ———
b) Non-Proprietary Name (USAN): Econazole Nitrate Cream, 1%

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug:	Spectazole® (econazole nitrate) Cream 1%
Holder:	Ortho Dermatological, Division of Ortho-McNeil Pharmaceutical, Inc. (Johnson & Johnson)
Application Number:	N 18-751
Strength:	1%
Patent Certification:	Paragraph II Certification (no unexpired patent)
Exclusivity:	None

10. PHARMACOL. CATEGORY: Antifungal agent

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _x__Rx ___OTC

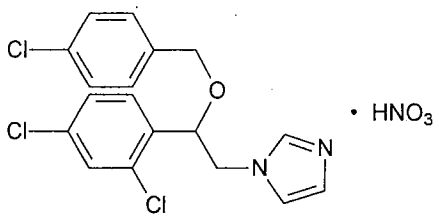
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x__Not a SPOTS product

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

1*H*-Imidazole, 1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-, mononitrate, (±)-. $C_{18}H_{15}Cl_3N_2O \cdot HNO_3$ Mol.wt. 444.7 CAS No. 68797-31-9



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3			
	III			4			
	IV			4			
	IV			4			

[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: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	4/28/03	J. D'Ambrogio
Methods Validation	N/A	--	See Item 31
Labeling	Acceptable	12/1/04	B. Weitzman
Bioequivalence	Acceptable	11/18/04	S. Ho
EA	Waiver		
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 76-574

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Not recommended for approval (pending Bio and Labeling).

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

II. Summary of Chemistry Assessments

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

The reference listed drug for this application is Spectazole® (econazole nitrate 1%) Cream by Ortho Dermatological Division of Ortho-McNeil Pharmaceutical, Inc. (Johnson & Johnson).

The drug substance is Econazole Nitrate, USP and conforms to the USP monograph. The drug substance is a white or almost white crystalline powder and is known to exist in only one polymorphic form.

The drug product is Econazole Nitrate Cream, 1% and is for topical application in the treatment of tinea pedis, tinea cruris, and tinea corporis. The drug product contains as excipients; Pegoxyl-7 Stearate, Mineral Oil, Peglicol 5 Oleate, Butylated Hydroxyanisole, Benzoic Acid and Purified Water.

The drug product is manufactured by [ ] and also provided specifications for release and stability.

The bulk drug product is packaged in 2 g (sample), 15 g, 30 g and 85 g blind-end ——lined aluminum tubes fitted with white polypropylene caps. The firm has requested a 24 month expiration date. The firm has provided satisfactory temperature cycling study results for the drug product.

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

N/A

C. Basis for Approvability or Not-Approval Recommendation

Labeling Acceptable
Bioequivalence Acceptable

III. Administrative

A. Reviewer's Signature

Bing Cai, Ph.D.

B. Endorsement Block

12/7/04

Chemist, B. Cai, Ph.D./HFD-620/01/30/04
Chemistry Team Leader, S. Liu, Ph.D/HFD-620 S.H.Liu 12/13/04
Project Manager, B. Danso, PharmD/HFD-617/12/7/04 BD 12/7/04

C. CC Block

ANDA #76-574
ANDA #76-574/Division File
Field Copy

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

cc: ANDA 76-574
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620 /Bcai, Ph.D./ 01/30/04

HFD-620/SLiu, Team Leader/ S.H. Liu 12/13/04

HFD-617/BDanso, PM/12/7/04 12/7/04

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TYPE OF LETTER:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-574

BIOEQUIVALENCE REVIEWS

Review of a Bioequivalence study with Clinical Endpoint

ANDA: 76-574
Drug Product: Econazole Nitrate Cream, 1%
Sponsor: Healthpoint, Ltd.
Reference Listed Drug: Spectazole® (Econazole Nitrate Cream, 1%), NDA 18-751
Reviewer: Sarah Ho, Pharm.D.
Submission dates: 12/16/02, 5/1/04
Date of Review: 11/3/04
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I. Introduction

Tinea Pedis

Tinea pedis, a fungal infection of the foot commonly known as athlete's foot, is most commonly caused by one or more of the following dermatophytes: *Trichophyton rubrum, Trichophyton metagrophytes* or *Epidermophyton floccosum*. The dermatophyte fungi invade the superficial keratin of the skin and remain in this layer, causing burning, itching, erythema, maceration, papules/pustules, scaling, and cracking of skin around the toes and soles of the feet.

Econzaole Nitrate

Spectazole® (Econazole Nitrate Cream, 1%) exhibits broad-spectrum antifungal activity and is indicated for topical application in the treatment of tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum, Trichophyton metagrophytes, Trichophyton tonsurans, Microsporum canis, Microsporum audouini, Microsporum gypseum* and *Epidermophyton floccosum,* in the treatment of cutaneous candidiasis, and in the treatment of tinea versicolor. Spectazole® should be applied to cover the affected areas once daily in patients with tinea pedis. Early relief of symptoms is experienced by the majority of patients and clinical improvement may be seen fairly soon after treatment has begun. For tinea pedis, treatment should be used for one month in order to reduce the possibility of recurrence.

II. Background

The following correspondence has been submitted to OGD regarding Econazole Nitrate Cream:

ANDA 76-005 (Taro Pharmaceuticals– approved November 26, 2002)
ANDA 76-075 (Altana, Inc. – approved November 26, 2002)
ANDA 76-479 (Clay-Park Labs, Inc. - approve June 23, 2004)
IND [redacted]
IND [redacted]
P00-033 (Healthpoint)

Healthpoint, Ltd. (Healthpoint) had submitted a protocol for Econazole Nitrate Cream, 1% (P00-033) that was reviewed by Dr. Mary Fanning in September of 2000. The protocol was found acceptable; however, there were a few comments which were communicated to the firm.

Healthpoint has made 5 amendments to their protocol (all dated after OGD issued comments on their original protocol.)

III. Study Information

Protocal Number: 735.113.CL004/01

Title: Bioequivalence Comparison of Generic Econazole Nitrate Cream, 1%, Spectazole® Cream, 1.0% compared to Generic Econazole Nitrate Cream Vehicle in the Treatment of Tinea Pedis.

Study Objective:

The purpose of this trial was to determine whether generic Econazole Nitrate Cream, 1% (test) is bioequivalent to Spectazole® Cream, 1.0% (reference) in the treatment of tinea pedis. Econazole Nitrate Cream Vehicle (vehicle) was used as a control. In addition, as part of the bioequivalence requirements, the active treatments must be superior to a vehicle control.

Study Design:

This study was conducted as a multicenter, randomized, investigator-blinded, active- and vehicle-controlled, parallel, 3-arm comparison involving patients with tinea pedis. Twelve study centers participated in this trial. The protocol called for the enrollment of approximately 428 (171:171:86) patients to obtain 116:116:58 evaluable patients for the two active products and vehicle, respectively. The following lots were used for this study:

- Generic Econazole Nitrate Cream, 1%: *REGP (30 g) & REGP-3 (85 g)*
- Spectazole® (econazole nitrate, 1.0%): *21G712 (30 g), 21A437 (30 g) & 22G858 (85 g)*
- Generic Econazole Nitrate Vehicle: *REGN (30 g), REGN-2 (30 g), REGN-4 (30 g) & SGFE-C (85 g)*

Patients treated the diseased area(s) of one or both feet once daily at bedtime for 28 days. The dosing instructions were identical to those specified in the approved labeling for Spectazole®. Patients were enrolled and evaluations were completed at Baseline and on Days 14, 28, and 42. If both feet were infected, the most severely affected foot was selected as the target foot. A specific area on the target foot was selected for evaluations.

Study Population:

Inclusion Criteria

Patients with all the following characteristics were eligible for study enrollment:

1. Male or female patients at least 18 years of age with tinea pedis;
2. Good general health confirmed by history and physical;
3. At least mild (score of 1 on a 4-point score system described under "Study Measurements") erythema, scaling, and pruritus;
4. Positive KOH (dermatophyte) observation of target foot;

5. Culture sample collected from the target foot and submitted for identification;
6. Female patients of childbearing potential with a negative pregnancy test;
7. Willing and capable of cooperating to the extent and degree required by the protocol; and
8. Signed an approved informed consent.

Reviewer's comment:

- *Baseline culture samples need to be positive in order for the patient to be included in the PP and MITT populations.*
- *According to the above inclusion criteria, the minimum baseline total score for all enrolled patients was 3. Although OGD customarily recommends a baseline total score of 4 for tinea pedis, the above criteria is acceptable given that the sponsor's definition of treatment success is very stringent.*

Exclusion Criteria

Patients with any of the following characteristics were NOT eligible for study enrollment:

1. Not undergone the specified washout period for topical corticosteroids or antifungal medications on the feet (14 days), any topical medication for tinea pedis (14 days), systemic corticosteroids or systemic antifungal medications (28 days);
2. Required ongoing concurrent systemic treatment with antifungal drugs or corticosteroids;
3. Severe hyperkeratotic plantar involvement of the target foot;
4. Diseases that would interfere with evaluations (e.g., uncontrolled diabetes, immunosuppression or psoriasis of the treatment area);
5. Extensive dermatophyte or other fungal diseases elsewhere on the body;
6. Inability to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function;
7. Female patients who were pregnant or nursing; and
8. Participation in another investigational study within the last 30 days.

Reviewer's comments: *Use of antipruritics, including antihistamines, within 72 hours of study entry may have affected baseline symptom scores. Those patients who used antipruritics or antihistamines within 72 hours of study entry should be excluded from both the MITT and PP populations.*

Concomitant/Prohibited Medications

Interfering therapies included all systemic or topical medications for tinea pedis (e.g., antifungal preparations and corticosteroids). All concurrent medications were recorded on the Concomitant Medication section of the Baseline visit form. Any medication started or changed after enrollment was entered on the Concomitant Medication Form. A corresponding Adverse Event form was completed for therapies added after enrollment. However, if a patient was treated with a different medication for an ongoing condition that was present at Baseline, completion of an Adverse Event form was not required unless the condition worsened.

Reviewer's comments:

- *If a patient was treated with a different medication for an ongoing condition that was present at Baseline, the new medication should have been recorded and verified that it was not an interdicted medication.*
- *Interfering therapies should include <u>any</u> systemic or topical antifungal medications and not just limited to tinea pedis.*
- *Use of antipruritics, including antihistamines, during the study period may interfere with the symptom scores during follow-up visit evaluations. Therefore, patients who used antipruritics during the study period should be excluded from the MITT and PP populations.*

<u>Instructions to Patients</u>

One application of the cream was applied at bedtime. Patients were instructed to avoid socks or other occlusive coverings and not to wash the foot for at least 8 hours.

<u>Criteria for Discontinuation of Patients</u>

Patients could be discontinued from the study for several reasons. They were:

1. Adverse event,
2. Treatment failure,
3. Noncompliance,
4. Prohibited medication,
5. Protocol violation,
6. Patient decision, or
7. Investigator decision related to patient safety,

Data from all patients who discontinued the study early are included in the ITT analyses of safety.

Reviewer's comment:

- *Those patients that discontinued from the study early due to insufficient treatment response ("treatment failure") should be included in the PP population as treatment failure for all analyses.*
- *Patients who did not return for the Day 42 visit should be excluded from the PP population. However, these patients should be included in the MITT population.*

<u>Randomization/Blinding:</u>

<u>Randomization</u>

Patients were randomly assigned, in chronological order of enrollment, to receive test, reference or vehicle. The randomization was according to a 2:2:1 ratio (171:171:86 patients) for test, reference or vehicle, respectively. The randomization code was prepared by [redacted].

Reviewer's comments: *Sealed randomization code should be kept at each study site and should be available to FDA investigators at the time of site inspection.*

Blinding

Identical labels were printed for this study. Each label contained the following information:

- Protocol number
- Patient number
- Space for the patient initials
- Space for the date of dispensing
- Dosing instructions
- Storage instructions
- Caution statement
- Sponsor identification and address

In addition, a "blind" label according to the patient assignment was supplied with the test articles. These labels contained a concealed listing of all ingredients as well as information provided on the affixed label described above. These "blind" labels were supplied in a separate envelope for emergency purposes only. The Investigator was to notify the sponsor immediately by phone if the blinded labels were opened for any reason. The envelopes were to remain unopened and kept with the test articles. None of the codes/labels were broken/opened and all were returned with other supplies upon study completion.

The test and vehicle products were supplied in identical tubes with identical labels. The reference product was not transferred into identical tubes. These reference product tubes were over-labeled with the same labels used for the other test articles. Although the labels were identical for all 3 test articles, the reference product tubes were distinguishable by appearance. Therefore, at least 2 staff members were required: one to dispense the tubes, and another to conduct the clinical evaluations. Both the person in charge of drug dispensation and the patient were instructed not to describe or show the assigned test article tube to the Investigator or other evaluator(s).

Study Procedures:

Measurements and visits related to the conduct of this study are listed below in a table format.

The firm amended their protocol on April 15, 2002 to state that visit windows were not to be used to eliminate patients from the PP Analysis.

Reviewer's comments: *Previous recommendations to the sponsor did not comment on visit windows. OGD has customarily recommended a visit window of ±4 days. Those patients who were outside the ±4 days for the Day 42 visit should be excluded from the PP population.*

Study Flow Chart

Procedures	Baseline	Day 14	Day 28	Day 42
Informed consent	X			
Demographics and history	X			
Inclusion/exclusion	X			
Urine Pregnancy Test (UPT)	X		X[b]	
KOH[a] and culture collection	KOH + Collect Culture		Examine KOH Collect Culture	Examine KOH Collect Culture
Disease severity	X			
Signs and symptoms of target area	X	X	X	X
Dispense test articles	X	X		
Weigh test articles	X	X	X	
Stop treatment			X	
Collect test articles		X	X	
Concomitant/concurrent medications	X	X	X	X
Adverse events	X	X	X	X

[a] Sample must be KOH positive for dermatophytes prior to study entry.
[b] Or sooner if discontinued.

Study Measurements

Severity Score-A 4-point score was used to assess global severity (i.e., the severity of the infection of the target foot, etc.) and the severity of erythema, scaling, pruritus, maceration, cracking/fissures, exudation and vesiculation, all hallmarks of tinea pedis. Each sign was scored 0 (none), 1 (mild), 2 (moderate), or 3 (severe). In addition, half point scores could be assigned to describe an observation that was intermediate of two scores.

Compliance-At each study visit after Baseline, patients were questioned regarding the number of doses applied since the last visit. Eighty percent compliance was required for inclusion in the PP analyses. Patients were required to bring their tube(s) to each study visit for general compliance review and inspection. On visit days 14 and 28, the number of missed doses was recorded. Patients who missed more than 6 doses (>20%) were considered noncompliant. The tubes were also weighed before and after use. These weights were recorded on the Drug Dispensation log.

Primary efficacy Variable - The target area (on the target foot) was evaluated at each visit. If both feet were infected, the Investigator evaluated/scored the foot that was more severely infected, as the target foot, at Baseline. All subsequent clinical assessments and mycological culture collections were performed on the target foot identified at Baseline. If only one foot was involved at Baseline and the other foot subsequently became infected during the study, the patient was discontinued because of an adverse event.

Statistical Plan:

Primary Endpoint

The primary efficacy endpoint was the percent of patients with Treatment success of the target area on Day 42 (2 week post-final-dose visit). Treatment success was defined as mycological cure and clinical signs and symptoms ≤ 0.5 on Day 42. Mycological cure was defined as the absence of fungal hyphae in a KOH preparation of skin scrapings and a negative mycological culture.

Reviewer's comment:

- *The usual primary endpoint accepted by FDA is therapeutic cure at 6 weeks (2 weeks after the end of treatment). Therapeutic cure is defined as mycologic cure (negative KOH smear and negative culture) and clinical cure (total severity score of no more than 2 with no individual severity score greater than 1). The sponsor's definition of treatment success is more stringent and acceptable.*
- *FDA has also accepted therapeutic cure at both 4 weeks and 6 weeks (i.e., those patients who have a therapeutic cure at 4 weeks and still have a therapeutic cure at 6 weeks), as this definition may reduce the "cure" rate by eliminating some patients with false negative cultures and may increase the power for demonstrating equivalence. However, the PP population may need to be defined differently for this combined endpoint.*
- *The statistical consultant is requested to analyze clinical cure, mycological cure and therapeutic cure at 4 week, at 6 weeks, and at both 4 and 6 weeks.*

Secondary Endpoint

Not specified. However, the sponsor did conduct a secondary analysis using the same populations as for the primary endpoint but on Day 28.

Reviewer's comments: *The usual secondary endpoints are therapeutic cure at end of treatment, clinical cure at end of treatment and at follow-up, mycological cure at end of treatment and at follow-up.*

Sample Size

In the original protocol, the sponsor estimated that approximately 120 patients per active treatment and 80 patients for the vehicle group were to be enrolled to obtain a sample size of 97 evaluable patients per active treatment and 49 for the vehicle.

On April 23, 2002, the protocol was amended to enroll 50 more patients because only 75% (instead of the expected 85%) of the subjects were culture-positive for dermatophytes at Baseline.

The protocol was amended again on August 15, 2002 to revise the sample size calculations to be as follows:

> Approximately 171 patients per active treatment were to be enrolled to obtain a sample size of 116 evaluable (PP) patients in order to provide at least an 80% probability of establishing bioequivalence of the active treatments by the 90% confidence interval

criteria under the assumption of an equivalent 45% clinical outcome success rate for both the test and reference products. Approximately 86 patients were to be enrolled in the vehicle group to obtain a sample size of 58 evaluable patients. A sample size of 116 evaluable patients per active treatment group and 58 evaluable patients for the vehicle group would have 90% power to detect superiority under the assumption that the clinical success rates are 45% and 20% for the active and vehicle groups, respectively.

Analysis

Baseline

The characteristics of the patients randomized to each treatment group at Baseline were compared. Continuous demographic variables at Baseline were examined by analysis of variance when normal error assumption was satisfied, or by the non-parametric Friedman's analysis of variance test when it was not, to compare treatment group differences. The Cochran-Mantel-Haenszel test, stratified by clinical site, was used for categorical variables such as gender and race.

Patient populations:

Three groups of patients were analyzed as described below. The primary efficacy analyses and results were based on the PP patient population followed by the MITT patient population. The ITT patient population was used for the safety analysis.

1. The Intent-to-Treat (ITT) group was used to evaluate safety. This group included all patients that received any test article.

2. The Modified Intent-to-Treat (MITT) group was used for the superiority analyses comparing the active treatments to the vehicle control. This subgroup included patients with clinical symptoms, a positive Baseline KOH (dermatophyte) observation and a positive Baseline culture (dermatophyte) result.

3. The Per-Protocol (PP) group was used for the bioequivalence analysis between the two active treatments. This subgroup included patients with clinical symptoms meeting the following criteria:
   - Those who were considered MITT with no *noteworthy* study protocol violations (e.g., patients continuing or starting an interfering therapy such as a systemic corticosteroid were excluded from this Per-Protocol group analyses);
   - Those who did not miss any study visits other than the Day 14 visit; and
   - Those who were compliant with the dosing regimen (i.e., patients received at least 80% of the specified treatments, patients did not miss more than six doses, etc.).

The data for patients discontinued prior to Day 42 were carried forward to the end-of-study time point for the MITT analyses. If a patient entered the study and was subsequently found to have a negative baseline culture result, that patient was dropped from efficacy evaluations (PP and MITT), but was included in the ITT safety evaluations.

Reviewer's comments:

- *Patients in the MITT population should also have had at least one dose of the medication and at least one follow-up visit.*
- *Patients who failed to return for one of the follow-up visits but came to the Day 42 visit should be included in the PP population for the primary endpoint. To be included in the PP population (for the primary endpoint analysis using only Day 42 visit), the patient could miss Day 28 visit.*
- *Patients with missing data for the Day 28 visit should be excluded in the PP population for the alternative primary endpoint analysis.*
- *Patients who discontinued the study early due to study drug related adverse event, other than treatment failure, should be excluded from the PP population. However, these patients should be included in the MITT population.*
- *As mentioned before, patients who discontinued the study early due to insufficient treatment response should be included in the PP population as treatment failure.*

Definition of Cure

1. Mycological cure was defined as the absence of fungal hyphae in a KOH preparation of skin scrapings and a negative mycological culture.
2. Treatment success was defined as mycological cure and clinical signs and symptoms <= 0.5 on Day 42 (2 week post-final-dose visit).

Reviewer's comments:

- *As stated above, the sponsor's definitions of mycologic and treatment cure are acceptable.*

Bioequivalence and Superiority

The clinical equivalence of the test article to the reference product was based on the proportion of patients who achieved a Treatment success at the post dose, two-week follow-up visit (Day 42). The primary therapeutic equivalence, Treatment success, of the test article to the reference product was established if the 90% confidence interval on the difference in their treatment success rates was contained within the interval -0.20 to +0.20. The 90% confidence interval was calculated by the sponsor using Wald's method with Yate's continuity correction.

The test for superiority of each active product over the test vehicle was based on the difference in treatment success rates (active-vehicle) at the Day 42 visit. Superiority was established by the sponsor if the lower limit of Wald's 95% confidence interval on this difference, with Yate's continuity correction, was greater than zero. There were two analyses of this type, one for each active, and in each analysis only the respective active treatment and vehicle were used.

The equivalence and superiority analyses were also performed at the end of the treatment on Day 28. These evaluations were considered as supportive to the primary evaluations for the Day 42 results.

Safety

All adverse events occurring during the study were recorded. Descriptions of events included the approximate date of onset, the date the adverse event ended, the severity of the adverse event, the relationship to study drug and the outcome. Comparisons between treatment groups were made by tabulating the frequency of patients with one or more adverse events (classified into COSTART terms) during the study. The Fisher's Exact test was used to compare the proportion of patients in each treatment group who reported any adverse event. The specific events analyzed were those that were reported by at least five percent of the patients in any treatment group. Pair wise comparisons were to be conducted if the overall comparison of the three treatment groups was significant.

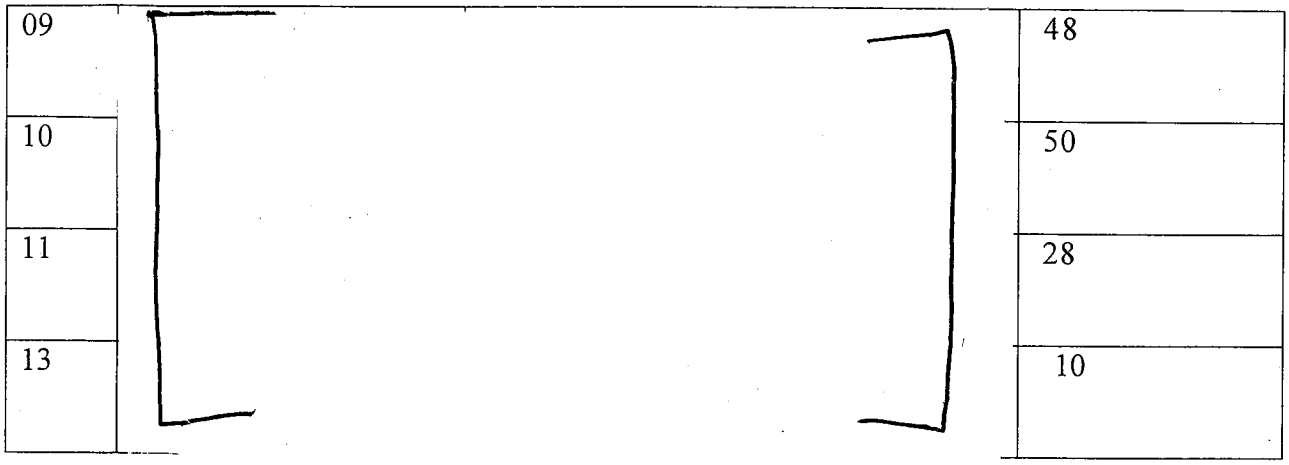
IV. Results

CRO: A CRO was not identified in the submission. However, Rainer Maas-Irslinger, M.D. (Medical Director of Healthpoint, Ltd.) was listed as "Principal or Coordinating Investigator or Sponsor's Responsible Medical Officer."

Study period:
First patient entered: August 22, 2001
Last patient completed: October 28, 2002

Study Center:

Site #	Investigator	Address	# patients enrolled
01			3
02			70
03			27
04			60
05			25
06			31
07			40
08			45



Study Enrollment

437 patients (test: 172, reference: 176, Vehicle: 89) were enrolled in the study and included in the safety ITT analyses. The sponsor reports that of the 437 patients enrolled, 405 completed and 32 were prematurely discontinued. According to the sponsor, nine (9) patients randomized to the test group discontinued from the study: four (4) due to an adverse event, three (3) lost to follow-up, one (1) patient request unrelated to an AE, and one (1) noncompliance. Fourteen (14) patients randomized to the reference group discontinued from the study: two (2) due to an adverse event, four (4) lost to follow-up, three (3) patient request unrelated to an AE, one (1) treatment failure, three (3) noncompliance, and one (1) patient was mistakenly discontinued due to a negative baseline culture. Nine (9) patients randomized to the vehicle group discontinued from the study: five (5) due to lost to follow-up, two (2) patient request unrelated to an AE, one (1) interfering therapy, and one (1) treatment failure.

Reviewer's Comments:

Per reviewer, the following additional patients in Table 1 should be excluded from the MITT and PP populations due to concomitant interdicted medication use prior to or during the study period.

In addition, patient 9023 does not meet exclusion criteria (an active, ongoing fungal infection of the fingernail at the time of enrollment) and should be excluded from the PP and MITT populations.

The following patients should be included in the PP population as treatment failure: 6004, 2002 and 3001. Patient 6004 used Lamisil cream due to worsened tinea pedis prior to Day 28 visit. Patients 2002 and 3001 discontinued from the study due to insufficient treatment response.

Table 1 - Additional patients to be excluded from MITT and PP populations for concomitant medication use (per reviewer)

Patient Number	*Medication*	*Time of use*
9008	*Lotrimin Cream*	*Prior to study period (< 14 days)*
1111	*Penlac (Ciclopirox Olamine)*	*Prior to and during study period*
1141	*Augmented betamethasone dipropionate*	*Prior to and during study period*
6002	*Locoid Cream (Hydrocortisone)*	*Prior to and during study period*
6030	*Hytone 2.5% (Hydrocortisone) & Lachydrin*	*Prior to and during study period*
1040, 1064, 3023, 8002	*Loratadine*	*Prior to and during study period*
3009, 8029	*Claritin*	*During study period*
1112	*Cetirizine*	*Prior to and during study period*
2006, 2023, 4001, 4011, 5016	*Fexofenadine*	*Prior to and during study period*
2024	*Tylenol Allergy Sinus & Sudafed cold and allergy*	*Prior to and during study period*
1138, 5039	*Drixoral*	*During study period*
1141	*Diprolene AF Cream*	*During study period*
2024	*Tavist-D*	*During study period*

Baseline Information
The sponsor has provided baseline information for the PP and MITT populations.

Demographics
Within the PP population, the sponsor reported that patients were evenly distributed at Baseline. There were no significant differences between treatment groups for the analysis of baseline demographic characteristics of age (p=0.656), race (p=0.823), and gender (p=0.947). In addition, there was not a statistically significant difference between treatment groups for the analysis of history of treatment success (p=0.187).

In the MITT population, the sponsor also reported that there were no significant differences between treatment groups for the analysis of Baseline demographic characteristics of age (p=0.904), race (p=0.680), and gender (p=0.769). There was not a statistically significant difference between treatment groups for the analysis of history of treatment success (p=0.150).

Microbial Organisms
According to the sponsor's analysis, most of the PP study population (249 patients/ 84%) were positive for *T rubrum.* Others were positive for *T mentagrophytes (28* patients/ 9%), *E.*

floccosum (18 patients/ 6%), or another dermatophyte (1 patient/ <1%). There was not an overall significant difference between groups for the analysis of Baseline culture (p=0.089).

In the MITT population, most (277 patients/ 84%) patients were positive for *T rubrum* and a few others were positive for *T. mentagrophytes* (31 patients/ 9%), *E. floccosum* (20 patients/ 6%), or another dermatophyte (1 patient/ <1%). There was not an overall significant difference between groups for the analysis of baseline culture (p=0.053).

Clinical Information

In the PP population, the sponsor reported that two hundred and twenty-three patients (75%) had a global severity of moderate upon enrollment at Baseline. The others were rated mild (19 patients/ 6%) and severe (54 patients/ 18%). There were no significant differences between treatment groups for the analysis of global severity at Baseline (p=0.227). In addition, there were no statistically significant differences between treatment groups regarding analysis of the key parameters erythema (p=0.191), scaling (p=0.112) and pruritus (p=0.882). There were no overall significant differences between treatment groups for the analysis of Baseline maceration (p=0.858), cracking/fissures (p=0.326), exudation (p=0.178), or vesiculation (p=0.895).

In the MITT population, the sponsor reported that two hundred and forty-seven patients (75%) had a global severity of moderate upon enrollment at Baseline. The others had a global severity of mild (21 patients/ 6 %) and severe (61 patients/ 19%). There were no significant differences between treatment groups for the analysis of global severity at Baseline (p=0.742). In addition, there were no statistically significant differences between treatments regarding analysis of the key parameters erythema (p=0.250), scaling (p=0.722) and pruritus (p=0.874). There was no overall significant difference between treatment groups for the analysis of baseline maceration (p=0.934), cracking/fissures (p=0.276), exudation (p=0.112), or vesiculation (p=0.755).

Reviewer's comments: *Table 2 below provides the baseline total severity score for all enrolled patients. Only 16 patients had a total severity score <4 at Baseline: 4 patients in the test group, 9 in the reference group, and 3 in the vehicle group.*

Table 2 - Total Severity Scores* at Baseline for All Enrolled Patients (per reviewer)

	Min	*Max*	*Mean*	*Std Deviation*
Test (N=172)	*3*	*18*	*6.65*	*2.31*
Reference (N=176)	*3*	*14.5*	*6.64*	*2.37*
Vehicle (N=89)	*3*	*14.5*	*6.71*	*2.23*

**Total severity score = sum of the individual sign and symptom severity scores for each patient.*

Efficacy Outcomes

Primary Endpoints

Bioequivalence

The analysis of treatment success on the per-protocol data set, at Day 42, is the primary analysis for bioequivalence. The PP data set analyzed at Day 28 is

supportive. Table 3 summarizes the results of the analysis of bioequivalence for treatment success for the PP patients at Day 42 and Day 28.

Treatment success was defined as mycological cure (negative KOH and culture), and clinical signs and symptoms less than or equal to 0.5 at Day 42. Refer to Table 3. Of the 119 patients in the test group, 56 (47%) were a treatment success according to the sponsor. Of the 117 patients in the reference group, 59 (50%) were a treatment success. Per the sponsor, the difference in success rates between the two treatments was -3.4% with a 90% confidence interval of -14.9% to 8.2%. According to the sponsor's analyses, the two active treatments were shown to be bioequivalent at Day 42 according to the PP data set.

In addition, the sponsor reported that the Day 28 PP data sets supported the Day 42 data analyses (refer to Table 3). Of the 119 per-protocol patients in the test group, 37 (31%) were a treatment success according to the sponsor. Of the 117 patients in the reference group, 42 (36%) were a treatment success. Once again, according to the sponsor the two active treatments are shown to be bioequivalent at Day 28. The difference in success rates between the two treatments, according to the PP data sets, was -4.8% with a 90% confidence interval of -15.7% to 6.1%.

Table 3 - Bioequivalence Analysis of Per-Protocol Population (per sponsor)

	Test		Reference			Confidence Intervals	
	N	TS*	N	TS*	Difference	Lower	Upper
Day 42	56	47.1%	59	50.4%	-3.4%	-14.9%	8.2%
Day 28	37	31.1%	42	35.9%	-4.8%	-15.7%	6.1%

*TS = Treatment Success

Efficacy

The modified intent-to-treat data sets for treatment success at Day 42 is the primary analysis for superiority. The MITT data set analyzed at Day 28 is supportive. Table 4 and Table 5 summarize the results of the sponsor's superiority analysis for treatment success at Day 42 and Day 28 of the active treatments compared to vehicle for the MITT patients.

Superiority was based on the difference in treatment success rates at Day 42 (MITT) between each active and the test vehicle. By Day 42, 59 of the 129 patients (46%) in the test group, 63 of the 132 patients (48%) in the reference group, and 6 of the 68 patients (9%) in the vehicle group were considered a treatment success by the sponsor. As shown in Table 4 (per sponsor), test was shown to be superior to its vehicle. The difference in success rates between test and its vehicle was 36.9% with a 95% confidence interval of 24.9% to 49.0% according to the sponsor's analysis. Reference was also shown to be superior to the vehicle by the sponsor (refer to Table 5 below). The difference in success rates between reference and vehicle was 38.9% with a 95% confidence interval of 26.9% to 50.9% according to the sponsor's analysis.

In addition, the sponsor reported that the Day 28 data sets (MITT) supported the Day 42 data analyses (refer to Table 4 and Table 5). Thirty-nine of the 129 patients (30%) in the test group, 47 of the 132 patients (36%) in the reference group, and 8 of the 68 patients (12%) in the vehicle group were considered a treatment success according to the sponsor. The difference in success rates between test and vehicle was 18.5% with a 95% confidence interval of 6.3% to 30.6% according to the sponsor's analysis, which demonstrates the superiority of test to vehicle. The difference in success rates between reference and vehicle was 23.8% with a 95% confidence interval of 11.5% to 36.2% according to the sponsor's analysis, which also demonstrates the superiority of reference to vehicle.

Table 4 - Superiority of Test vs. Vehicle in the Modified-Intent-To-Treat Population (per sponsor)

	Test		Vehicle			Confidence Intervals	
	N	TS*	N	TS*	Difference	Lower	Upper
Day 42	59	45.7%	6	8.8%	36.9%	24.9%	49.0%
Day 28	39	30.2%	8	11.8%	18.5%	6.3%	30.6%

*TS = Treatment Success

Table 5 - Superiority of Reference vs. Vehicle in the Modified-Intent-To-Treat Population (per sponsor)

	Reference		Vehicle			Confidence Intervals	
	N	TS*	N	TS*	Difference	Lower	Upper
Day 42	63	47.7%	6	8.8%	38.9%	26.9%	50.9%
Day 28	47	35.6%	8	11.8%	23.8%	11.5%	36.2%

*TS = Treatment Success

Adverse Events

According to the sponsor, there were no serious treatment-related or unexpected adverse events reported during the study. There were only three serious adverse events (unrelated to the study drug) reported by the sponsor. Patient 9024 (in the test group) had unrelated elective surgery for a penile implant for sexual dysfunction. Patient 1111 (also in the test group) experienced serious events of pyelonephritis and dehydration during the study period. These events resolved with treatment and were considered to be definitely unrelated to the study drug by the sponsor. Patient 6004 reported cellulitis during the study period. This event also resolved with treatment and was considered unrelated to the study drug.

The sponsor reported the analysis of adverse events for those adverse events reported by at least 5% of patients in any treatment group. In order to protect the overall type I error rate, pairwise treatment comparisons of the adverse event analyses were considered statistically significant only when the overall test was significant. There was not a significant difference between treatment groups for the number of patients reporting events ($p=0.693$). Nor was there a significant difference between treatment groups for the body systems body as a whole ($p=0.186$), respiratory system ($p=0.730$), or skin ($p=0.067$). There were also no significant differences between treatment groups for the specific events of headache ($p=0.502$) or infection ($p=0.399$).

Reviewer's comments:

- *The sponsor did not report the number of patients who discontinued from the study due to adverse events. From the data set provided by the sponsor, six patients were reported to have discontinued from the study as a result of adverse events. The three patients mentioned above discontinued from the study. In addition, three other patients were discontinued from the study. Patient 1061 (in the reference group) experienced severe pruritis of both feet and subsequently discontinued from the study. Patient 2001 (in the test group) reported blisters on his toes that was determined to be possibly related to the study medication. Patient 2001 also discontinued from the study. Patient 3004 (in the reference group) developed tinea pedis in the contralateral foot and was discontinued from the study. Patient 3004's adverse event was determined to be unrelated to the study medication.*
- *The Reference Listed Drug's (RLD) labeling reports that 3% of patients treated with econazole nitrate cream, 1% reported sides effects consisting mainly of burning, itching, stinging, and erythema. According to the data set provided by the sponsor, this reviewer's analysis shows that 4.07% (7) of the patients in the test group reported skin related adverse events. In the reference group, 1.14% (2) and in the vehicle group, 1.16% (1). the actual number of patients who experienced the adverse events is small and the percentage of patients in the test group with skin related adverse events is similar to that reported in the RLD's labeling. Given that the test product contains the same active and inactive ingredients as the RLD and in nearly identical amounts, it is unlikely that the small differences in skin-related adverse events observed in this study represent a significant difference in irritation potential.*

V. Formulation

Ingredients	Test - Qty % (w/w)	Reference* - Qty % (w/w)
Econazole Nitrate USP	1.00	1
Peglicol 5 Oleate		
Butylated Hydroxyanisole NF		
Benzoic Acid USP		
Mineral Oil USP		
Pegoxol 7 Stearate		
Purified Water USP		

*Formulation information obtained from COMIS (NDA 18-751).

Retention Samples
Not specified.

Reviewer's comment: *It is a requirement of the United States Food and Drug Administration (under 21 CFR 320.38 and 320.63) that samples of the study drug be kept at the investigator's office or another secure location for a length of time after the study is completed. The purpose of this regulation is to assure the FDA that the study was conducted with the stated study drug. Samples of each study drug were to be randomly selected from each drug shipment and were to be kept as "retention samples".*

VI. Review of Division of Scientific Investigation (DSI) report
A request for investigation was submitted on March 22, 2004.

DSI conducted three clinical site inspections (EIR review dated October 7, 2004). All three sites have been classified as VAI (Voluntary Action Indicated). During the inspections, DSI issued FDA Form 483 to each site. It was noted that the sites understood the observations noted on Form 483 and agreed to make efforts to prevent such occurrences in the future.

The objectionable findings are as follows:
1. Two of the sites did not meet regulatory requirements regarding bioequivalence testing samples (21 CFR Parts 320.38 and 320.63). The number of samples selected at each site was not sufficient to meet the requirements set forth in the guidance.
2. One site failed to exclude 7 patients who did not have the appropriate washout periods following corticosteroid or antifungal treatment.
3. One site failed to document the test drug kit number dispensed to 47 out of 60 patients.

Reviewer's Comments:
- *It is the sponsor's responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63. If the sponsor fails to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.*
- *Of the 7 patients that the site did not exclude due to inappropriate washout periods, 6 patients (Patients 1107, 1109, 1111, 1112, 9007 and 9008) were already excluded from the FDA MITT and PP populations. A statistical reanalysis was requested to exclude the 7th patient (Patient 1110) from the MITT and PP populations.*
- *A statistical reanalysis was requested to exclude the 47 patients whose test drug kit numbers were not recorded. Furthermore, the investigator provided additional information in response to the DSI deficiencies, explaining that the kit numbers corresponded to the patient numbers and that the drug assignments had been documented elsewhere.*
- *Given that DSI categorized these deficiencies as VAI (voluntary action indicated),the remainder of the data from this study need not be discarded due to these deficiencies.*

VII. Review of the FDA Statistical Report
The following instructions were forwarded to the statistician:
1. *Baseline culture samples need to be positive in order for the patient to be included in the PP and MITT populations.*
2. *Those patients that discontinued from the study early due to insufficient treatment response ("treatment failure") should be included in the PP population as treatment failure for all analysis.*
3. *Patients who did not return for the Day 42 visit should be excluded from the PP population. However, these patients should be included in the MITT population.*
4. *Previous recommendations to the sponsor did not comment on visit windows. OGD has customarily recommended a visit window of ±4 days. Those patients who were outside the ±4 days for the Day 42 visit should be excluded from the PP population.*

5. *The usual primary endpoint accepted by FDA is therapeutic cure at 6 weeks (2 weeks after the end of treatment). Therapeutic cure is defined as mycologic cure (negative KOH smear and negative culture) and clinical cure (total severity score of no more than 2 with no individual severity score greater than 1). The sponsor's definition of treatment success is more stringent and acceptable. FDA has also accepted therapeutic cure at both 4 weeks and 6 weeks (i.e., those patients who have a therapeutic cure at 4 weeks and still have a therapeutic cure at 6 weeks), as this definition may reduce the "cure" rate by eliminating some patients with false negative cultures and may increase the power for demonstrating equivalence. However, the PP population may need to be defined differently for this combined endpoint. The statistical consultant is requested to analyze clinical cure, mycological cure and therapeutic cure at 4 week, at 6 weeks, and at both 4 and 6 weeks.*
6. *The usual secondary endpoints are therapeutic cure at end of treatment, clinical cure at end of treatment and at follow-up, mycological cure at end of treatment and at follow-up.*
7. *Patients in the MITT population should also have had at least one dose of the medication and at least one follow-up visit.*
8. *Patients who failed to return for one of the follow-up visits but came to the Day 42 visit should be included in the PP population for the primary endpoint. To be included in the PP population (for the primary endpoint analysis using only Day 42 visit), the patient could miss Day 28 visit.*
9. *Patients with missing data for the Day 28 visit should be excluded in the PP population for the alternative primary endpoint analysis.*
10. *Patients who discontinued the study early due to study drug related adverse event, other than treatment failure, should be excluded from the PP population. However, these patients should be included in the MITT population.*
11. *The following patients should be excluded from the MITT and PP populations due to interdicted medication use: 9008, 1111, 1141, 6002, 6030, 1040, 1064, 3023, 8002, 3009, 8029, 1112, 2006, 2023, 4001, 4011, 5016, 2024, 1138, 5039, 1141, 2024.*
12. *Patient 9023 did not meet exclusion criteria (an active, ongoing fungal infection of the fingernail at the time of enrollment) and should be excluded from the PP and MITT populations.*
13. *The following patients should be included in the PP population as treatment failure: 6004, 2002 and 3001.*

Addendum (4/29/04)
The following 6 patients should be excluded from the PP populations (but included in the MITT population): 1054, 1061, 2001, 3004, 6004, and 9024. These patients discontinued the study early due to study drug related adverse events, other than treatment failure.

Addendum (10/25/04)
As a result of the DSI inspection findings, an additional reanalysis of Healthpoint's data was requested excluding 47 out of 60 patients (patients numbers provided in the EIR Review dated October 7, 2004) from Site #04 and Patient 1110 from the ITT and PP populations.

The FDA statistical analyses supported the bioequivalence of the test and the reference products. The original analyses showed that the 90% CI of therapeutic cure at the Day 42 (2 week post-

final-dose visit) endpoint (-13.1, 12.5) for the PP population was within -.20 and +.20. The test and the reference products also demonstrated superiority ($p<0.05$) over Placebo in the ITT population for therapeutic cure at the Day 42 endpoint ($p<0.001$).

The additional FDA statistical analyses (to exclude 47 patients from Site #4 and Patient 1110) also supported the bioequivalence of the test and the reference products. The re-analyses showed that the 90% CI of therapeutic cure at the Day 42 endpoint (-15.1, 12.4) for the PP population was within -.20 and +.20. The test and the reference products also demonstrated superiority ($p<0.05$) over Placebo in the ITT population for therapeutic cure at the Day 42 endpoint ($p<0.001$).

VIII. Conclusion

The data presented in this ANDA demonstrate that Healthpoint, Ltd.'s Econazole Nitrate Cream, 1% is bioequivalent to the reference listed drug Spectazole® Cream.

IX. Recommendation

The data submitted to ANDA 76-574, using the primary endpoint of therapeutic cure rate at Day 42 (2 week post-final-dose visit) are adequate to demonstrate bioequivalence of Healthpoint, Ltd.'s Econazole Nitrate Cream, 1% with the reference listed drug, Spectazole® Cream. This application is recommended for approval from a clinical bioequivalence standpoint.

X. Comments to be conveyed to the Sponsor

1. It is the sponsor's responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63. Please refer to the "Guidance for Industry: Handling and Retention of BA and BE Testing Samples, May 2004" for additional information. If the sponsor fails to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.
2. It is the sponsor's responsibility to oversee all the clinical sites and the investigators to assure that the protocol is adhered to and proper documentations are made for all future BE studies.

Sarah Ho, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

11/8/04
Date

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

11/8/04
Date

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

11/18/04
Date

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-574 APPLICANT: Healthpoint, Ltd.

DRUG PRODUCT: Econazole Nitrate Cream, 1%

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

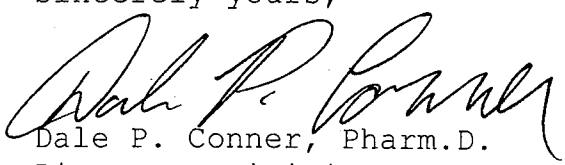
The data submitted to ANDA 76-574, using the primary endpoint of therapeutic cure rate at the 2 week follow-up visit (day 42), are adequate to demonstrate bioequivalence of Healthpoint, Ltd.'s Econazole Nitrate Cream, 1% with the reference listed drug, Spectazole®.

It is the sponsor's responsibility to assure that the clinical sites for all future BE studies comply with the requirements for retention of study drugs as per 21 CFR 320.38 and 320.63. Please refer to the "Guidance for Industry: Handling and Retention of BA and BE Testing Samples, May 2004" for additional information. If the sponsor fails to comply with the Agency's regulation in any subsequent study, the study may be found unacceptable and a new bioequivalence study may be requested.

It is the sponsor's responsibility to oversee all the clinical sites and the investigators to assure that the protocol is adhered to and proper documentations are made for all future BE studies.

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

Sincerely yours,



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

CC: ANDA 76-574
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ S. Ho
HGD-600/ D. Hixon

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Endorsements: (Final with Dates)
HFD-600/S. Ho 11/8/04
HFD-600/D. Hixon 11/8/04
HFD-650/D. Conner 11/18/04

BIOEQUIVALENCY - ACCEPTABLE

submission dates:
December 16, 2002
May 1, 2004

1. Bioequivalence Study (STU); December 16, 2002 Strengths: 1%
Outcome: AC

2. Study Amendments (STA); May 1, 2004 Strengths: 1%
Outcome: AC

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

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-574 SPONSOR : Healthpoint, Ltd.

DRUG AND DOSAGE FORM : Econazole Nitrate Cream

STRENGTH(S) : 1%

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites in United States

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status: Complete	Inspection results: VAI, acceptable
First Generic ____ New facility __X__ For cause ____ other ____	Inspection requested: (date) 3/22/2004 Inspection completed: (date) 10/7/2004	

PRIMARY REVIEWER: Sarah Ho, Pharm. D.

INITIAL : _____ DATE : 11/8/04

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

INITIAL : _____ DATE : 11/8/04

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

INITIAL : _____ DATE : 11/18/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-574

STATISTICAL REVIEWS

ANDA 76-574
Drug Product: Econazole Nitrate Cream 1%
Sponsor: Healthpoint ltd.
Reference Listed Drug: Spectazole@ (Econazole Nitrate Cream 1%)
Johnson and Johnson, Inc., NDA 18-751
Submission date: 6/16/02
V:/firmsam/healthpo/ltrs&rev/76574st.doc

Reviewer: Huaixiang Li, Ph.D., QMRS/OB/CDER
Requestor: Dena Hixon, MD, Sarah Ho, Pharm.D., OGD/CDER, 4/22/04

Objectives of the study

The primary objective of the study was to establish the bioequivalence of the test product, Healthpoint ltd., Econazole Nitrate cream 1%, and the reference product, Johnson and Johnson, Inc., Spectazole@ cream, and to show superiority of the two active treatments to the placebo, a cream vehicle, in the treatment of tinea pedis.

Remarks

The sponsor submitted SAS datasets and programs to the Office of Generic Drugs (OGD), CDER on 12/02/2002, and an additional dataset to the Electronic Document Room (EDR), CDER on 5/1/2004. The statistical analyses used information from four datasets: 'h735113.xpt', 'mycology.xpt', 'ptstatu2.xpt', and 'ptstats2.xpt'.

The following adjustments to these submitted datasets were made in accordance with recommendations of the FDA medical reviewers and our (medical and statistical reviewers) best judgment.[1]

Exclusion/inclusion from the FDA's Intent-to-treat (FITT)/Per protocol (FPP) populations

1) Nine patients, three (1081, 2027, 8021) in the test treatment group, three (2039, 3010, 8031) in the reference treatment group, and three (1143, 7005, 8034) in the placebo group, were excluded from the FITT population due to no post baseline visit.

2) Patient 1001 in the placebo group was excluded from the FITT population due to having violated the inclusion criteria (pruritus score=0.5 at baseline).

3) Nineteen patients, eight in the test treatment group, six in the reference treatment group, and five in the placebo group, were excluded from the FITT and FPP populations due to concomitant medication use. Patient #8029 in the reference treatment group was excluded from the FITT population due to concomitant medication use.

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

4) Two patients, 3004 in the test treatment group and 6004 in the reference treatment group, who discontinued due to study drug related adverse events, were included in the FITT population.

5) Two patients, 3001 in the reference treatment group and 2002 in the placebo group, who discontinued early due to treatment failure, were included in the FPP population as treatment failures.

6) The visit windows, 28±4 days at visit 3 (Day 28) and 42±4 days at visit 4 (Day 42), were used for the FPP population. Thirty-eight patients, 11 in the test treatment group, 17 in the reference treatment group, and 10 in the placebo group, were excluded from the FPP population due to out of the visit window(s).

Evaluation/revision of the success/cure rates at Day 28 and Day 42 visits

1) The dataset submitted by the sponsor only contained the therapeutic cure at visit 3 (Day 28) and at visit 4 (Day 42). The clinical cure and mycological cure at visit 3 and at visit 4 (assessed independently per each visit), and the clinical cure, mycological cure, and therapeutic cure at both visit 3 and 4 (two visits combined) were evaluated by the FDA statistical reviewer.

2) Mycological cure requires a negative KOH observation and a negative fungal culture. Three patients, #1030 in the test treatment group at visit 4, #3012 in the placebo group at visit 4, and #3025 in the reference treatment group at visit 3, had missing KOH observations and negative culture results. They were re-coded as missing instead of cure as coded in the original dataset.

3) Patients who had one or more missing measurements (signs/symptoms, KOH, culture results) were re-coded as missing, instead of failure as coded in the original dataset. The Last observation Carried Forward (LOCF) method was used to carry the data from visit 3 to visit 4 for the FDA's Intent-to-treat (FITT) population when the data was missing at visit 4. Fourteen patients, 2 in the test treatment group, 9 in the reference treatment group, and 3 in the placebo group were re-coded for therapeutic result(s) at either visit 3 or visit 4, or both visits.

Study Design

This was a 3 arm parallel double-blind study for patients with signs and symptoms of tinea pedis. The three creams were the test product, Healthpoint ltd., Econazole Nitrate cream 1%, the reference product, Johnson and Johnson, Inc., Spectazole@ cream, and the placebo, a cream vehicle.

A total of 437 patients were enrolled and randomly assigned to three treatment groups in the study with a ratio of 2:2:1 (test:reference:placebo). At the baseline visit (Day 1), the patients with clinical signs and symptoms of tinea pedis had a skin scraping taken from an area of active lesions for KOH mount and fungal culture. The signs/symptoms,

erythema, scaling, pruritus, maceration, cracking/fissures, exudation, and vesticulation, were measured by using a score (0-3, none to severe, with half scores permitted).

For inclusion in the study, the patient had to have at least mild (score of ≥ 1 on 0-3 score level) for each erythema, scaling, and pruritus sign/symptom, positive KOH result and met the eligibility criteria. The eligible patient was instructed to apply the study cream to the affected area once daily for four weeks. Patients returned for clinical evaluations at visit 2 (Day 14), visit 3 (Day 28 – end of treatment visit), and visit 4 (Day 42 – follow-up visit). The mycological evaluation (both KOH and fungal culture tests) was performed at visit 3 and 4. The signs/symptoms were measured at each visit.

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.
Per-protocol population (PP) – All subjects in the ITT population who completed the study and were evaluable for the analyses based on the protocol, FDA medical and statistical reviewers' best judgment.

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

Outcome Variables at Visit 3 (Day 28) and Visit 4 (Day 42)

The primary efficacy variable was therapeutic cure at visit 4.

The secondary efficacy variables were

- therapeutic cure at visit 3
- clinical cure and mycological cure (assessed independently) at visit 4
- clinical cure and mycological cure (assessed independently) at visit 3
- clinical cure, mycological cure, and therapeutic cure at both visit 3 and 4 (two visits combined).

The sponsor defined clinical cure as each signs/symptoms score less than or equal to 0.5 in this study. The FDA medical reviewer noted, *"The usual primary endpoint accepted by FDA is therapeutic cure at 6 weeks (2 weeks after the end of treatment). Therapeutic cure is defined as mycological cure (negative KOH smear and negative culture) and clinical cure (total severity score of no more than 2 with no individual severity score greater than 1). The sponsor's definition of treatment success is more stringent and acceptable."* A further check verified that patients who had each signs/symptoms score less than or equal to 0.5 also had a total severity score of no more than 2 in this study.

The three cures were defined in this study as:

clinical cure - each signs/symptoms score less than or equal to 0.5,
mycological cure - negative KOH observation and negative fungal culture,
therapeutic cure – both a clinical cure and a mycological cure.

Statistical Analysis Methods

Efficacy Analysis

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

The efficacy analyses for the clinical cure rate, mycological cure rate, and therapeutic cure rate were carried out by using Fisher's exact test (two-sided) for each active treatment versus placebo with a significance level of α=0.05. The active treatments should be more distinguishable from placebo as the study progressed.

Equivalence Analysis

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

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -.20$

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.

Statistical Analysis Results

A total of 437 patients were enrolled. The FDA's ITT population included 301 patients and the FDA's PP population included 241 patients.

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

	Econazole	Spectazole®	Placebo	Total
Enrollment	**172**	**176**	**89**	**437**
Negative baseline culture	42	44	20	106
Inclusion/exclusion criteria violation	1	0	1*@	2
Testing medical kit dispensed incorrectly	0	0	1	1
No post baseline visit*@	3	3	3	9
Concomitant medication use*	8	7	5	20
Inclusion in FITT population*	+1	+1	0	+2
Total exclusions from FITT population	53	53	30	136
FDA's ITT population (FITT)	**119**	**123**	**59**	**301**
Sponsor's MITT population	*129*	*132*	*68*	*329*
No Day 28 and/or Day 42 visit	5	7	3	15
No Day 42 culture	2	5	1	8
Discontinued due to study drug related adverse events (3004)#	1	0	0	1
Inclusion into FPP population as treatment failure#	0	+1	+1	+2
Out visit window at visit 3 (day 28±4) and/or 4 (day 42±4)#	11	17	10	38
Total exclusions from FDA's PP population	19	28	13	60
FDA's PP population (FPP)	**100**	**95**	**46**	**241**
Sponsor's PP population	*119*	*117*	*60*	*296*

&: Patient(s) may have multiple reasons to be excluded from the MITT, PP, FITT, and FPP populations.
*: Patient(s) was excluded from or included in the FITT population.
@: These patients were included in the sponsor's MITT population, but excluded from the sponsor's PP population.
#: Patient(s) was excluded from or included in the FPP population.

Demographics and baseline

The mean age was 42.6 years and the age ranged from 18 to 83 years old in the FITT population. The table below shows the sex and race distribution for the FITT population. The age, sex, and race of patients were comparably distributed among the three treatment groups for the FITT and FPP populations, based on chi-square tests.

	Econazole	Spectazole®	Placebo	Total
Sex				
Female	32	35	14	81
Male	87	88	45	220
Race				
White	80	85	40	205
Black	11	13	7	31
Others	28	25	12	65

An analysis of the frequencies and chi-square tests for homogeneity of signs/symptoms scores for the FITT and FPP 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

Remark: The total numbers of patients in the analyses sometimes were less than the numbers in the populations, due to missing values.

Primary endpoints: Therapeutic cure rate at visit 4.

Efficacy and equivalence analyses for primary 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%)
FITT	46.6 (55/118)	49.6 (58/117)	8.8 (5/57)	<0.001	<0.001		
FPP	46.0 (46/100)	46.3 (44/95)	8.9 (4/45)			-13.1, 12.5	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 (2-sided).

The two active treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the FPP population for the therapeutic cure rate at visit 4.

Secondary endpoints: therapeutic cure at visit 3; clinical cure and mycological cure (assessed independently) at visit 3 and at visit 4; clinical cure, mycological cure, and therapeutic cure at both visit 3 and 4 (two visits combined)

Efficacy and equivalence analyses for secondary endpoints

Population	Test % successes (No. of successes)	Reference % successes (No. of successes)	Placebo % successes (No. of successes)	p-value for Test vs. Placebo	p-value for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
FITT	N=119	N=123	N=59				
Visit 3							
Clinical cure	41.0 (48/117)	47.1 (56/119)	28.1 (16/57)	*0.131*	0.022		
Mycological cure	59.8 (70/117)	54.7 (64/117)	24.6 (14/57)	<0.001	<0.001		
Therapeutic cure	31.6 (37/117)	36.8 (43/117)	14.0 (8/57)	0.016	0.002		
Visit 4							
Clinical cure	55.9 (66/118)	57.5 (69/120)	22.8 (13/57)	<0.001	<0.001		
Mycological cure	71.2 (84/118)	70.9 (83/117)	17.5 (10/57)	<0.001	<0.001		
Visit 3 and 4							
Clinical cure	35.8 (42/117)	41.2 (49/119)	19.3 (11/57)	0.035	0.004		
Mycological cure	53.0 (62/117)	43.6 (51/117)	12.3 (7/57)	<0.001	<0.001		
Therapeutic cure	28.2 (33/117)	29.9 (35/117)	5.3 (3/57)	<0.001	<0.001		
FPP	N=100	N=95	N=46				
Visit 3							
Clinical cure	41.0 (41/100)	43.2 (41/95)	28.3 (13/46)			-14.8, 10.5	Yes
Mycological cure	59.0 (59/100)	53.7 (51/95)	28.3 (13/46)			-7.4, 18.0	Yes
Therapeutic cure	31.0 (31/100)	33.7 (32/95)	17.4 (8/46)			-14.7, 9.4	Yes
Visit 4							
Clinical cure	55.0 (55/100)	52.6 (50/95)	21.7 (10/46)			-10.4, 15.1	Yes
Mycological cure	72.0 (72/100)	71.6 (68/95)	20.0 (9/45)			-11.2, 12.1	Yes
Visit 3 and 4							
Clinical cure	35.0 (35/100)	36.8 (35/95)	19.6 (9/46)			-14.2, 10.5	Yes
Mycological cure	52.0 (52/100)	43.2 (41/95)	15.6 (7/45)			*-3.9, 21.6*	*No*
Therapeutic cure	27.0 (27/100)	27.4 (26/95)	6.7 (3/45)			-11.9, 11.1	Yes

The two active treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the FPP population for all of the secondary endpoints except two cases. The test product was better, but not statistically significantly better than placebo for clinical cure for the FITT population at visit 3. The equivalence test was failed for the mycological cure rate at visit 3 and 4 (two visits combined) for the FPP population, with a greater success rate for the test product than for the reference product.

Comments on the Sponsor's Analysis

The sponsor's analysis results using their MITT and PP populations for the total cure rate based on their definition mentioned above were summarized in the FDA medical review's report (page 14-15). The two active treatments were statistically significantly better than placebo for the MITT population and the equivalence test was passed for the PP population for the sponsor's total cure rate. The differences between our results and the sponsor's were due to the adjustment to the datasets in accordance with recommendations of the OGD medical reviewers and our (medical and statistical reviewers) best judgment.

Safety

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

Conclusion

Primary endpoint: therapeutic cure rate at visit 4 (Day 42 – follow-up visit)

The two active treatments were significantly better than placebo for the FDA's ITT (FITT) population and the equivalence test was passed for the FDA's PP (FPP) populations.

Secondary endpoints: therapeutic cure at visit 3 (Day 28 – end of treatment visit); clinical cure and mycological cure (assessed independently) at visit 3 and at visit 4; clinical cure, mycological cure, and therapeutic cure at both visit 3 and 4 (two visits combined)

The two active treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the FPP population for all of secondary endpoints except two cases. The test product was better, but not statistically significantly better than placebo for clinical cure for the FITT population at visit 3. The equivalence test was failed for the mycological cure rate at visit 3 and 4 (two visits combined) for the FPP population, with a greater success rate for the test product than for the reference product.

Huaixiang Li 7/7/04
Huaixiang Li, Ph.D.
Mathematical Statistician, QMR

Donald J. Schuirmann 7/7/04
Donald J. Schuirmann
Expert Mathematical Statistician, QMR

Stella G. Machado
Stella G. Machado, Ph.D. 7/8/04
Director, QMR

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

ANDA 76-574
Drug Product: Econazole Nitrate Cream 1%
Sponsor: Healthpoint ltd.
Reference Listed Drug: Spectazole@ (Econazole Nitrate Cream 1%)
Johnson and Johnson, Inc., NDA 18-751
Submission date: 6/16/02
V:/firmsam/healthpo/ltrs&rev/76574stad.doc

Reviewer: Huaixiang Li, Ph.D., QMRS/OB/CDER
Requestor: Dena Hixon, MD, Sarah Ho, Pharm.D., OGD/CDER, 4/22/04

Additional analysis

At the request of HFD-650, the Division of Scientific Investigations conducted an audit of this study. The following two concerns will affect the statistical analysis.

Exclusion from the FDA's Intent-to-treat (FITT)/Per protocol (FPP) populations

1) Thirty-six patients in Site 4, nineteen (1070, 1072,1075,1127,1130,1134, 4004, 4005, 4008, 4010, 4014, 4015, 4018, 4021, 4023, 4028, 4034, 4035, 4037) in the test treatment group, thirteen (1071, 1073, 1128, 1132, 4002, 4006, 4013, 4019, 4022, 4025, 4026, 4031, 4032) in the reference treatment group, and four (1126, 4003, 4024, 4029) in the placebo group, were excluded from the FITT population due to failing to document the drug kit number dispensed to the patients. Consequently, thirty-one patients out of these patients (31 out of 36) were excluded from FPP populations. Five patients, two (1134 and 4037) in the test treatment group, three (1071, 4002, 4006) in the reference treatment group were already excluded from FPP population for the previous analysis.

2) Patient 1110 (Site 9) in the test treatment group was excluded from the FITT population due to use of treatments during the washout period.

Statistical Analysis Results

A total of 437 patients were enrolled. The FDA's ITT population included 264 patients and the FDA's PP population included 210 patients.

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

	Econazole	Spectazole®	Placebo	Total
Enrollment	**172**	**176**	**89**	**437**
FDA's ITT population (FITT)	**99**	**110**	**55**	**264**
FDA's PP population (FPP	**83**	**85**	**42**	**210**
FDA's ITT population (FITT- 1st review)	119	123	59	301
FDA's PP population (FPP- 1st review)	100	95	46	241
Sponsor's MITT population	*129*	*132*	*68*	*329*
Sponsor's PP population	*119*	*117*	*60*	*296*

Demographics and baseline

The mean age was 42.6 years and the age ranged from 18 to 83 years old in the FITT population. The table below shows the sex and race distribution for the FITT population. The age, sex, and race of patients were comparably distributed among the three treatment groups for the FITT and FPP populations, based on chi-square tests.

	Econazole	Spectazole®	Placebo	Total
Sex				
Female	28	30	12	70
Male	71	80	43	194
Race				
White	63	73	36	172
Black	10	13	7	30
Others	26	24	12	62

An analysis of the frequencies and chi-square tests for homogeneity of signs/symptoms scores for the FITT and FPP 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

Remark: The total numbers of patients in the analyses sometimes were less than the numbers in the populations, due to missing values.

Primary endpoints: Therapeutic cure rate at visit 4.

Efficacy and equivalence analyses for primary 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%)
FITT	42.9 (42/98)	47.1 (49/104)	7.5 (4/53)	<0.001	<0.001		
FPP	42.2 (35/83)	43.5 (37/85)	7.3 (3/41)			-15.1, 12.4	Yes

*: The rate of success equals the number of successes divided by the total number, then multiplied by 100.
#: The p-values were from Fisher's exact test (2-sided).

The two active treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the FPP population for the therapeutic cure rate at visit 4.

Secondary endpoints: therapeutic cure at visit 3; clinical cure and mycological cure (assessed independently) at visit 3 and at visit 4; clinical cure, mycological cure, and therapeutic cure at both visit 3 and 4 (two visits combined)

Efficacy and equivalence analyses for secondary endpoints

Population	Test % successes (No. of successes)	Reference % successes (No. of successes)	Placebo % successes (No. of successes)	p-value for Test vs. Placebo	p-value for Reference vs. Placebo	90% Confidence interval for Test vs. Ref. (%)	90% CI is within (-20%, 20%)
FITT	N=99	N=110	N=55				
Visit 3							
Clinical cure	36.7 (36/98)	43.4 (46/106)	26.4 (14/53)	*0.211*	0.039		
Mycological cure	59.2 (58/98)	52.9 (55/104)	22.6 (12/53)	<0.001	<0.001		
Therapeutic cure	27.6 (27/98)	33.7 (35/104)	11.3 (6/53)	0.024	0.002		
Visit 4							
Clinical cure	53.1 (52/98)	54.2 (58/107)	20.8 (11/53)	<0.001	<0.001		
Mycological cure	68.4 (67/98)	71.2 (74/104)	17.0 (9/53)	<0.001	<0.001		
Visit 3 and 4							
Clinical cure	32.7 (32/98)	37.7 (40/106)	17.0 (9/53)	*0.054*	0.010		
Mycological cure	52.0 (51/98)	43.3 (45/104)	11.3 (6/53)	<0.001	<0.001		
Therapeutic cure	25.5 (25/98)	27.9 (29/104)	3.8 (2/53)	<0.001	<0.001		
FPP	N=83	N=85	N=42				
Visit 3							
Clinical cure	36.1 (30/83)	40.0 (34/85)	26.2 (11/42)			-17.4, 9.7	Yes
Mycological cure	57.8 (48/83)	52.9 (45/85)	26.2 (11/42)			-8.9, 18.7	Yes
Therapeutic cure	26.5 (22/83)	31.8 (27/85)	14.3 (6/42)			-18.0, 7.4	Yes
Visit 4							
Clinical cure	51.8 (43/83)	49.4 (42/85)	19.1 (8/42)			-11.5, 16.3	Yes
Mycological cure	68.7 (57/83)	71.8 (61/85)	19.5 (8/41)			-15.9, 9.7	Yes
Visit 3 and 4							
Clinical cure	31.3 (26/83)	34.1 (29/85)	16.7 (7/42)			-15.9, 10.3	Yes
Mycological cure	50.6 (42/83)	43.5 (37/85)	14.6 (6/41)			*-6.8, 20.9*	*No*
Therapeutic cure	24.1 (20/83)	25.9 (22/85)	4.9 (2/41)			-14.0, 10.4	Yes

The two active treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the FPP population for all of the secondary endpoints except three cases. The test product was better, but not statistically significantly better than placebo for clinical cure for the FITT population at visit 3 and at visit 3 and 4 (two visits combined). The equivalence test was failed for the mycological cure rate at visit 3 and 4 (two visits combined) for the FPP population, with a greater success rate for the test product than for the reference product.

Conclusion

Primary endpoint: therapeutic cure rate at visit 4 (Day 42 – follow-up visit)

The two active treatments were statistically significantly better than placebo for the FDA's ITT (FITT) population and the equivalence test was passed for the FDA's PP (FPP) population.

Secondary endpoints: therapeutic cure at visit 3 (Day 28 – end of treatment visit); clinical cure and mycological cure (assessed independently) at visit 3 and at visit 4; clinical cure, mycological cure, and therapeutic cure at both visit 3 and 4 (two visits combined)

The two active treatments were statistically significantly better than placebo for the FITT population and the equivalence test was passed for the FPP population for all of secondary endpoints except three cases. The test product was better, but not statistically significantly better than placebo for clinical cure for the FITT population at visit 3 and at visit 3 and 4 (two visits combined). The equivalence test was failed for the mycological cure rate at visit 3 and 4 (two visits combined) for the FPP population, with a greater success rate for the test product than for the reference product.

Huaixiang Li

Huaixiang Li, Ph.D.
Mathematical Statistician, QMR

Donald J. Schuirmann 12/13/04

Donald J. Schuirmann
Expert Mathematical Statistician, QMR

Stella G. Machado

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-574

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

Reference is made to deficiency letter dated December 1, 2003, and minor amendment dated December 19, 2003.

Reference is also made to deficiency 2C:

We have the following concerns regarding the drug product release specifications:

[redacted]

In your original application the decimal was off by one decimal point for product release. In your amendment dated December 19, 2003, the error was corrected; however, the specification range is still not consistent. Moreover, the [redacted] specification for bulk is also inconsistent. Please clarify both specifications.

Firm: We will provide the final range of the specification for both bulk and release in a telephone amendment.

DATE:
February 26, 2004

ANDA NUMBER:
76-574

PRODUCT NAME:
Econazole Nitrate Cream, 1%

INITIATED BY:

Firm __ **Agency**_X_

FIRM NAME:
Healthpoint, Ltd.

FIRM REPRESENTATIVE:
Kay Mary Harrell

TELEPHONE NUMBER:
210-476-8184

FDA REPRESENTATIVE:
Shing Liu, Ph.D.
Bing Cai, Ph.D.
Wanda Pamphile, Pharm.D.

SIGNATURE
Shing Liu S. H. Liu 2/26/04
Bing Cai
Wanda Pamphile 2/26/04

Orig: ANDA 76-574
Cc: Division File
Chem. I
V:\FIRMSAM\HEALTHPO\TELECONS\76574.doc

RECORD OF TELEPHONE CONVERSATION

On this date, I contacted Healthpoint, Ltd. (Healthpoint) to request the following: 1. Please explain the notation of "L" found in many of the variable in the datasets. 2. Please provide a summary of the PP and MITT populations and the reasons for exclusion from each population. Specifically the number of patients in each population and the number of patients excluded for each reason. 3. In addition, please provide the reason for exclusion from the PP and MITT populations for each patient. I instructed Ms. Woodward to submit Healthpoint's response as a Bioequivalence Amendment in paper and electronic formats. Ms. Woordward agreed to do so.	**DATE:** 4/28/04 **ANDA NUMBER** 76-574 **TELECON INITIATED BY SPONSOR** **PRODUCT NAME:** Econazole Nitrate Cream, 1% **FIRM NAME:** Healthpoint, Ltd. **FIRM REPRESENTATIVES:** Bobbi Woodward, Regulatory Affairs Director **TELEPHONE NUMBER:** 817-916-2307 **FDA REPRESENTATIVES** Sarah Ho **SIGNATURES:** S.Ho 11/22/04

Orig: ANDA 76-574
Cc: Division File

V:\FIRMSAM\HEALTHPO\TELECONS\76574.28apr2004.doc

OGD APPROVAL ROUTING SUMMARY

ANDA Nbr: 76-574 Applicant: Healthpoint, Ltd
Drug: Econazole Nitrate Cream Strength(s): 1%

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

REVIEWER: **DRAFT Package** **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date _____ Initials _____
Date 12/7/04 Initials RWT for

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)

Determ. of Involvement? Yes ☐ No ☒

Pediatric Exclusivity System:
RLD: Spectazole Cream, 1%
NDA#: N/A
Date Checked:
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
Date settled: _____

Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification, did applicant
notify patent holder/NDA holder: Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter:
Comments: Recommended for approval - no unexpired patents/exclusivity.

2. Project Manager, Ben Danso Team: 5
Review Support Branch
Date 12/7/04 Initials BD
Date _____ Initials _____

Original Rec'd date: 16-Dec-2002
Date Acceptable for Filing: 17-Dec-2002
Patent Certification (type): P III
Date Patent/Exclus.expires _____
Citizens Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic: NO
Acceptable Bio Reviews Tabbed Yes ☒ No ☐
Suitability Petition/Pediatric Wavier
Pediatric Wavier Request: Accepted ☐ Rejected ☐ Pending

EER Status: Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/28/2003
Date of Office Bio Review 11/18/2004
Date of Labeling Approv. Sum 12/01/2004
Date of Sterility Assur. Apprvd. _____
Methods Val. Samples Pending: Yes ☐ No ☐
M.V. Commitment Rec'd. from Firm: Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐ No ☐

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

3. Div. Dir./~~Deputy Dir~~.
Chemistry Div. I, ~~II, or III~~
Comments:
Date 12/13/04
Initials RK

The CMC section is satisfactory.

4. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
NDA, ANDA, for this drug product have previously been approved for Taro, Caraark, and Altana.

REVIEWER: **FINAL ACTION**

5. Gregg Davis Date_____
Deputy Dir., DLPS Initials_____
RLD= Spectazole Cream 1% NDA 18751
Johnson and Johnson Consumer Companies, Inc.

6. Peter Rickman Date 12/17/04 (for
Director, DLPS Initials Robert West)
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Bioequivalence review (multi-site clinical study) found acceptable 11/8/04. Statistical review also completed and DSI inspections completed. Office level biowaiver 11/8/04. FPL found acceptable 12/1/04. CMC found acceptable for approval 12/13/04. Methods validation for the drug product was not requested (NDA is compendial).

6. Robert L. West Date 12/17/2004
Deputy Director, OGD Initials (Robert West)
Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments: Acceptable EES dated 4/28/05 (verified 12/17/04). NDO.A.I. checks noted. There are no unexpired patents or exclusivities currently listed in the Orange Book for this drug product.

This ANDA is recommended for approval.

7. Gary Buehler
Director, OGD
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

Date 12/17/04
Initials

8. Project Manager, Team Ben Danso
Review Support Branch

Date 12/17/04
Initials BD

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

Applicant notification:
9:41 am Time notified of approval by phone 9:50 am Time approval letter faxed

FDA Notification:
12/17/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
12/17/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-574

CORRESPONDENCE

HEALTHPOINT

318 McCULLOUGH
SAN ANTONIO, TX 78215
210.476.8184
FAX 210.227.6132

11/5/03
Ack for filing
505(j)(2)(A)
S. Middleton

505(j)(2)(A) OK
17-JAN-2003
Gregory P. Davis

KAY MARY HARRELL
DIRECTOR, REGULATORY AFFAIRS

December 16, 2002

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-630)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

Via Federal Express

Re: ANDA submission for ——— (econazole nitrate) Cream 1%

Dear Mr. Buehler:

Enclosed please find the archival and review copies of the Abbreviated New Drug Application for ——— (econazole nitrate) Cream 1% and three additional copies of the method validation. The listed reference drug for this application is Spectazole® (econazole nitrate) Cream 1%. The applicant/sponsor is Healthpoint, Ltd., and the manufacturer is DPT Laboratories, Ltd.

In accordance with the requirements of 21 CFR 314.94(d)(5), I hereby certify that a field copy of the application has been sent today by first class mail to the FDA Dallas District Office.

Correspondence regarding this application may be directed to Kay Mary Harrell, Healthpoint, Ltd., 318 McCullough St., San Antonio, Texas 78215 (telephone 210-476-8184; fax 210-227-6132).

Thank you for your prompt handling of this submission.

Very truly yours,

Kay Mary Harrell

Kay Mary Harrell

ANDA 76-574

Healthpoint, Ltd.
Attention: Mark A. Mitchell
318 McCullough
San Antonio, TX 78215

JAN 17 2003

Dear Sir:

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 January 16, 2003 and your correspondence dated January 16, 2003.

NAME OF DRUG: Econazole Nitrate Cream, 1%

DATE OF APPLICATION: December 16, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 17, 2002

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

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

Should you have questions concerning this application, contact:

Sarah Ho
Project Manager
(301) 827-5848

Sincerely yours,

Gregory K. Davis for

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

HEALTHPOINT

318 McCULLOUGH
SAN ANTONIO, TX 78215
210.476.8184
FAX 210.227.6132

ORIG AMENDMENT
N/AM

KAY MARY HARRELL
DIRECTOR, REGULATORY AFFAIRS

September 5, 2003

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-630)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855
Attention: Wanda Pamphile, Project Manager (210-827-5763)

Via Federal Express

Re: ANDA 76-574 Econazole Nitrate Cream 1%
MINOR AMENDMENT- Response to Chemistry Deficiencies

Dear Mr. Buehler:

Enclosed please find the original and two copies of the Minor Amendment in response to FDA chemistry deficiencies dated May 13, 2003 for the Abbreviated New Drug Application for Econazole Nitrate Cream 1%. The listed reference drug for this application is Spectazole® (econazole nitrate) Cream 1%. The applicant/sponsor is Healthpoint, Ltd., and the manufacturer is DPT Laboratories, Ltd.

In accordance with the requirements of 21 CFR 314.94(d)(5), I hereby certify that a field copy of the application has been sent today by first class mail to the FDA Dallas District Office.

Correspondence regarding this application may be directed to Ms. Bobbi Woodward, Healthpoint, Ltd., 3909 Hulen St., Ft. Worth, Texas 76107 (telephone 817-916-2307; fax 817-900-4107).

Thank you for your prompt handling of this submission.

RECEIVED
SEP 0 8 2003
OGD/GDEB

Very truly yours,

Kay Mary Harrell

ANDA 76-574

Healthpoint Ltd.
Attention: Mark A. Mitchell
318 McCullough
San Antonio, TX 78215

DEC 12

Dear Sir:

This is in reference to your pending abbreviated new drug application Econazole Nitrate Cream 1%.

Please note that our laboratory is planning to conduct research studies on bioequivalency of some Econazole Nitrate topical drug products. These include both approved drug products and those under review by the Agency. Therefore, the Office of Generic Drugs needs 25 tubes of the largest size of your drug product, 100 gm of the active drug substance, 25 tubes of the placebo product and 25 tubes of the Innovator product, if available. Your prompt response to this request would be appreciated.

Please forward the requested product samples to the following address:

Office of Generic Drugs, CDER, FDA
Attention: Ann Vu
Metro Park North II, 7500 Standish Place
Rockville, MD 20855

When the samples are shipped to OGD, please forward a cover letter to Ms Vu indicating the date it was shipped. Please identify the sample containers with proper information on the immediate container label, such as the Name of the drug product, Strength, Batch number, Date manufactured, Certificate of Analysis, Proposed expiration dating period, Storage conditions, and the Name and Address of the applicant. Please note that OGD will pay the cost for samples if a bill is enclosed in the shipping box. Thank you in advance.

Sincerely yours,

James M. Farr for 12/10/03

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

HEALTHPOINT®

3909 HULEN STREET
FORT WORTH, TEXAS 76107
817.900.4000
800.441.8227
CUSTOMER CARE FAX 817.900.4100

ORIG AMENDMENT
N/AM

RECEIVED
DEC 23 2003
MEGA/CDER

December 19, 2003

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-630)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855
Attention: Wanda Pamphile, Project Manager (210-827-5763)

Via Federal Express

RE: ANDA 76-574 – Econazole Nitrate Cream 1%
MINOR AMENDMENT – Response to Chemistry Deficiencies

Dear Mr. Buehler:

Enclosed please find the original and two copies of the Minor Amendment in response to FDA chemistry deficiencies dated December 1, 2003 for the Abbreviated New Drug Application for Econazole Nitrate Cream 1%. The listed reference drug for this application is Spectazole® (econazole nitrate) Cream 1%. The applicant/sponsor is Healthpoint, Ltd., and the manufacturer is DPT Laboratories, Ltd.

In accordance with the requirements of 21 CFR 314.94(d)(5), I hereby certify that a field copy of the application has been sent today by first class mail to the FDA Dallas District Office.

Thank you for your prompt handling of this submission. If there are any questions, please feel free to contact me directly.

Sincerely,

Bobbi Woodward

Bobbi Woodward, MS, RAC
Director, Regulatory Affairs
Phone: (817) 916-2307
Fax: (817) 900-4107

RECEIVED
DEC 24 2003
OGD/CL...

HEALTHPOINT

318 McCULLOUGH
SAN ANTONIO, TX 78215
210.223.3281
FAX 210.227.6132

3.1

ORIG AMENDMENT
N/AM

February 26, 2004

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-630)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855
Attention: Wanda Pamphile, Project Manager (301-827-5763)

Via FAX to Wanda Pamphile (301) 594-0180
Via Federal Express

RE: ANDA 76-574 – Econazole Nitrate Cream 1%
TELEPHONE AMENDMENT – Response to Chemistry Deficiencies

Dear Mr. Buehler:

In the response to the telephone request on February 26, 2004 enclosed please find the revised specifications tables for "[redacted] Drug Product Specifications" in Appendix III of the December 19, 2003 Minor Ammendment for the Abbreviated New Drug Application for Econazole Nitrate Cream 1%. The revised specifications clarify the specifications for [redacted] The Bulk specification range is [redacted] and the Finished Release range is [redacted].

In accordance with the requirements of 21 CFR 314.94(d)(5), I hereby certify that a field copy of the application has been sent today by first class mail to the FDA Dallas District Office.

Thank you for your prompt handling of this submission. If there are any questions, please feel free to contact me directly.

Sincerely,

Bobbi Woodward
By: [illegible]

Bobbi Woodward, MS, RAC
Director, Regulatory Affairs
Phone: (817) 916-2307
Fax: (817) 900-4107

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ORIG AMENDMENT

NIAB

May 1, 2004

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-630)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855
Attention: Sarah Ho (301-827-5754)

Via FAX to Sarah Ho (301) 594-0180
Via Federal Express

RE: ANDA 76-574 – Econazole Nitrate Cream 1%
TELEPHONE AMENDMENT – Response to Bioequivalence Questions

Dear Mr. Buehler:

In the response to the telephone request on April 28, 2004 enclosed please find the response to the Bioequivalence questions asked. The SAS data set has also been provided as requested.

Thank you for your prompt handling of this submission. If there are any questions, please feel free to contact me directly.

Sincerely,

Bobbi Woodward

Bobbi Woodward, MS, RAC
Director, Regulatory Affairs
Phone: (817) 916-2307
Fax: (817) 916-2300

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November 12, 2004

DRUG AMENDMENT
N/AM

Mr. Gary Buehler
Director, Office of Generic Drugs (HFD-630)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855
Attention: Wanda Pamphile

Via FAX to Wanda Pamphile (301) 594-0180
Via Federal Express

RE: ANDA 76-574 – Econazole Nitrate Cream 1%
TELEPHONE AMENDMENT – Response to Chemistry Deficiencies

Dear Mr. Buehler:

In the response to the telephone request of November 5, 2004 enclosed please find the proposed labeling for Econazole Nitrate Cream, 1%. This amendment includes the package insert, and both tube and carton artwork for the 2g, 15g, 30g, and 85g tube sizes.

Thank you for your prompt handling of this submission. If there are any questions, please feel free to contact me directly.

Sincerely,

Bobbi Woodward

Bobbi Woodward, MS, RAC
Director, Regulatory Affairs
Phone: (817) 916-2307
Fax: (817) 900-4107

Attachments

RECEIVED
NOV 15 2004
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