

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-633

Name: Fluticasone Propionate Cream, 0.05%

Sponsor: Atrix Laboratories, Inc.

Approval Date: May 14, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-633

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-633

APPROVAL LETTER

ANDA 76-633

MAY 14 2004

Atrix Laboratories, Inc.
Attention: Cheri Jones
2579 Midpoint Drive
Fort Collins, CO 80525-4417

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 31, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluticasone Propionate Cream, 0.05%.

Reference is also made to the Tentative Approval letter issued by this office on April 26, 2003, and your amendment dated April 27, 2004.

We have completed the review of this tentatively approved 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 Fluticasone Propionate Cream, 0.05%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Cutivate[®] Cream, 0.05%, of GlaxoSmithKline).

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,



Gary Buehler 5/14/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-633
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:

HFD-620/B.Lim

HFD-620/S.Liu

HFD-617/W.Pamphile

HFD-613/B.Weitzman

HFD-613/J.Grace

RL 5/10/04
S.H. Liu 5/10/04
W.P. 5/10/04
B.W. 5/10/04
J.G. 5/10/04

*5/11/04
related*

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F/T by

APPROVAL

*Robert West
5/12/2004
pending expiration of
6SK's exclusivity on 5/14/04*

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-633

TENTATIVE APPROVAL LETTER

APR 26 2004

Atrix Laboratories, Inc.
Attention: Cheri Jones
2579 Midpoint Drive
Fort Collins, CO 80525

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 31, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fluticasone Propionate Cream, 0.05%.

Reference is also made to your amendments dated December 5, 2003; and February 3, February 19, March 10, and April 22, 2004.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, as noted in detail below, we are unable to grant final approval to your application at this time. Thus, your application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product. The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Cutivate Cream of GlaxoSmithKline, was subject to a period of patent protection. As noted in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. patent 4,335,121 (the '121 patent) expired on November 14, 2003.

Your application contains a Paragraph III Certification to the '121 patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the

expiration of this patent. However, the expiration of the '121 patent has effectively been extended by a period of marketing exclusivity under Section 111 of Title 1 of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). The Modernization Act created section 505(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). Section 505(A) permits certain applications to obtain up to an additional 6-months of marketing exclusivity (pediatric exclusivity) if, in accordance with the requirements of the statute, the NDA sponsor submits requested information relating to the use of the drug product in a pediatric population. GlaxoSmithKline (GSK) submitted such information to the Agency. These data were reviewed and it was determined that the data met the criteria stated in the statute. Thus, GSK was awarded 6-months of pediatric exclusivity for Cutivate Cream. Since the pediatric data were submitted prior to the November 14, 2003, expiration of the '121 patent, 6-months was added to the former expiration date of the patent. This action effectively extended the '121 patent until May 14, 2004. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the exclusivity period has expired, i.e., May 14, 2004.

In order to reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" upon receipt of this tentative approval letter. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. This submission should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

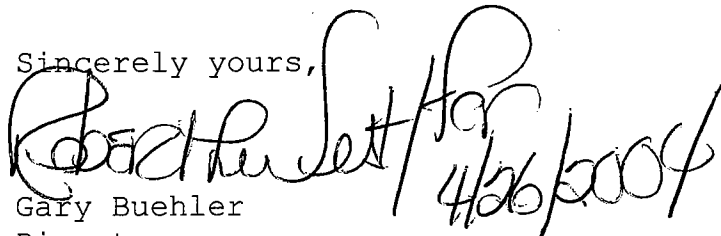
Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

This drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to May 14, 2004, you should amend your application accordingly.

At the time you submit any amendments, please contact Wanda Pamphile, Pharm.D., Project Manager, at 301-827-5848, for further instructions.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Gary Buehler", followed by a vertical line and the date "4/26/2004".

Gary Buehler

Director

Office of Generic Drugs

Center for Drug Evaluation and Research

cc: ANDA 76-633
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-92

Endorsements:

HFD-620/B.Lim

HFD-620/S.Liu

HFD-617/W.Pamphile

HFD-613/B.Weitzman

HFD-613/J.Grace

B.Lim 4/21/04

S.H. Liu 4/21/04

WP 4/21/04

BW 4/19/04

JG 4/19/04

*TA
RF
4/23/04*

*Robert West
4/26/2004*

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F/T by: wp 4/16/04

TENTATIVE APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-633

APPROVED LABELING

demonstrated fluticasone propionate to be teratogenic (cleft palate) when administered subcutaneously in doses of 45 mcg/kg per day and 150 mcg/kg per day. This dose is approximately 14 and 45 times, respectively, the human topical dose of fluticasone propionate cream, 0.05%. There are no adequate and well-controlled studies in pregnant women. Fluticasone Propionate Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Fluticasone Propionate Cream is administered to a nursing woman.

Pediatric Use: Fluticasone Propionate Cream may be used with caution in pediatric patients as young as 3 months of age. The safety and efficacy of drug use for longer than 4 weeks in this population have not been established. The safety and efficacy of Fluticasone Propionate Cream in pediatric patients below 3 months of age have not been established.

Fluticasone propionate cream, 0.05%, caused HPA axis suppression in 2 of 43 pediatric patients, ages 2 and 5 years old, who were treated for 4 weeks covering at least 35% of the body surface area. Follow-up testing 12 days after treatment discontinuation, available for 1 of the 2 subjects, demonstrated a normally responsive HPA axis (see ADVERSE REACTIONS). Adverse effects including striae have been reported with use of topical corticosteroids in pediatric patients.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels to an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Geriatric Use: A limited number of patients above 65 years of age (n = 126) have been treated with Fluticasone Propionate Cream in US and non-US clinical trials. While the number of patients is too small to permit separate analysis of efficacy and safety, the adverse reactions reported in this population were similar to those reported by younger patients. Based on available data, no adjustment of dosage of Fluticasone Propionate Cream in geriatric patients is warranted.

ADVERSE REACTIONS: In controlled clinical trials of twice-daily administration, the total incidence of adverse reactions associated with the use of Fluticasone Propionate Cream was approximately 4%. These adverse reactions were usually mild; self-limiting; and consisted primarily of pruritus, dryness, numbness of fingers, and burning. These events occurred in 2.9%, 1.2%, 1.0%, and 0.6% of patients, respectively.

Two clinical studies compared once- to twice-daily administration of Fluticasone Propionate Cream for the treatment of moderate to severe eczema. The local drug-related adverse events for the 491 patients enrolled in both studies are shown in Table 1. In the study enrolling both adult and pediatric patients, the incidence of local adverse events in the 119 pediatric patients ages 1 to 12 years was comparable to the 140 patients ages 13 to 62 years.

Fifty-one pediatric patients ages 3 months to 5 years, with moderate to severe eczema, were enrolled in an open-label HPA axis safety study. Fluticasone Propionate Cream was applied twice daily for 3 to 4 weeks over an arithmetic mean body surface area of 64% (range, 35% to 95%). The mean morning cortisol levels with standard deviations before treatment (prestimulation mean value = 13.76 ± 6.94 mcg/dL, poststimulation mean value = 30.53 ± 7.23 mcg/dL) and at end treatment (prestimulation mean value = 12.32 ± 6.92 mcg/dL, poststimulation mean value = 28.84 ± 7.16 mcg/dL) showed little change. In 2 of 43 (4.7%) patients with end-treatment results, peak cortisol levels following cosyntropin stimulation testing were <18 µg/dL, indicating adrenal suppression. Follow-up testing after treatment discontinuation, available for 1 of the 2 subjects, demonstrated a normally responsive HPA axis. Local drug-related adverse events were transient burning, resolving the same day it was reported; transient urticaria, resolving the same day it was reported; erythematous rash; dusky erythema, resolving within 1 month after cessation of Fluticasone Propionate Cream; and telangiectasia, resolving within 3 months after stopping fluticasone propionate cream.

Table 1: Drug-Related Adverse Events – Skin

Adverse Events	Fluticasone Once Daily (n = 210)	Fluticasone Twice Daily (n = 203)	Vehicle Twice Daily (n = 78)
Skin infection	1 (0.5%)	0	0
Infected eczema	1 (0.5%)	2 (1.0%)	0
Viral warts	0	1 (0.5%)	0
Herpes simplex	0	1 (0.5%)	0
Impetigo	1 (0.5%)	0	0
Atopic dermatitis	1 (0.5%)	0	0
Eczema	1 (0.5%)	0	0
Exacerbation of eczema	4 (1.9%)	1 (0.5%)	1 (1.3%)
Erythema	0	2 (1.0%)	0
Burning	2 (1.0%)	2 (1.0%)	2 (2.6%)
Stinging	0	2 (1.0%)	1 (1.3%)
Skin irritation	6 (2.9%)	2 (1.0%)	0
Pruritus	2 (1.0%)	4 (1.9%)	4 (5.1%)
Exacerbation of pruritus	4 (1.9%)	1 (0.5%)	1 (1.3%)
Folliculitis	1 (0.5%)	1 (0.5%)	0
Blisters	0	1 (0.5%)	0
Dryness of skin	3 (1.4%)	1 (0.5%)	0

Table 2: Adverse Events * From Pediatric Open-Label Trial (n = 51)

Adverse Events	Fluticasone Twice Daily
Burning	1 (2.0%)
Dusky erythema	1 (2.0%)
Erythematous rash	1 (2.0%)
Facial telangiectasia†	2 (4.9%)
Non-facial telangiectasia	1 (2.0%)
Urticaria	1 (2.0%)

*See text for additional detail.
†n = 41.

The following local adverse reactions have been reported infrequently with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and miliaria. Also, there are reports of the development of pustular psoriasis from chronic plaque

psoriasis following reduction or discontinuation of potent topical corticosteroid products.

OVERDOSAGE: Topically applied Fluticasone Propionate Cream can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION: Fluticasone Propionate Cream may be used in adult and pediatric patients 3 months of age or older. Safety and efficacy of Fluticasone Propionate Cream in pediatric patients for more than 4 weeks of use have not been established (see PRECAUTIONS: Pediatric Use). The safety and efficacy of Fluticasone Propionate Cream in pediatric patients below 3 months of age have not been established.

Atopic Dermatitis: Apply a thin film of Fluticasone Propionate Cream to the affected skin areas once or twice daily. Rub in gently.

Other Corticosteroid-Responsive Dermatoses: Apply a thin film of Fluticasone Propionate Cream to the affected skin areas twice daily. Rub in gently.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Fluticasone Propionate Cream should not be used with occlusive dressings. Fluticasone Propionate Cream should not be applied in the diaper area, as diapers or plastic pants may constitute occlusive dressings.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with Fluticasone Propionate Cream, safety did not differ from that in younger patients; therefore, no dosage adjustment is recommended.

CLINICAL STUDIES:

Psoriasis Studies: In 2 vehicle-controlled studies, Fluticasone Propionate Cream applied twice daily was significantly more effective than the vehicle in the treatment of moderate to severe psoriasis. The investigator's global evaluation after 28 days of treatment is shown in Table 3.

Table 3: Physician's Assessment of Clinical Response

	Fluticasone Propionate Cream		Vehicle	
	Study 1 (n = 59)	Study 2 (n = 74)	Study 1 (n = 66)	Study 2 (n = 75)
Cleared	8%	1%	3%	1%
Excellent	29%	28%	11%	17%
Good	27%	34%	20%	28%
Fair	27%	15%	33%	25%
Poor	7%	22%	24%	27%
Worse	2%	0	9%	1%

The clinical signs of psoriasis were scored on a scale of 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The mean improvements over baseline in the clinical signs at the end of treatment are shown in Table 4.

Table 4: Clinical Signs: Mean Improvements Over Baseline

	Fluticasone Propionate Cream		Vehicle	
	Study 1	Study 2	Study 1	Study 2
Erythema	1.19	1.07	0.55	0.84
Thickening	1.22	1.17	0.81	0.97
Scaling	1.53	1.39	0.95	1.21

Atopic Dermatitis Studies: In 2 controlled 28-day studies, Fluticasone Propionate Cream once daily was equivalent to Fluticasone Propionate Cream twice daily in the treatment of moderate to severe eczema. The investigator's global evaluation after 28 days of treatment is shown in Table 5.

Table 5: Physician's Assessment of Clinical Response

	Fluticasone Propionate Cream Once Daily		Fluticasone Propionate Cream Twice Daily	
	Study 1 (n = 64)	Study 2 (n = 106)	Study 1 (n = 65)	Study 2 (n = 100)
Cleared	30%	20%	48%	21%
Excellent	42%	32%	32%	50%
Good	17%	26%	5%	12%
Fair	3%	14%	6%	10%
Poor	5%	3%	8%	4%
Worse	3%	6%	2%	3%

The clinical signs and symptoms of atopic dermatitis were scored on a scale of 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The mean improvements over baseline at the end of treatment are shown in Table 6.

Table 6: Clinical Signs and Symptoms: Mean Improvements Over Baseline

	Fluticasone Propionate Cream Once Daily		Fluticasone Propionate Cream Twice Daily	
	Study 1	Study 2	Study 1	Study 2
Erythema	1.7	1.5	1.8	1.7
Pruritus	2.1	1.6	2.1	1.7
Thickening	1.6	1.3	1.6	1.5
Lichenification	1.2	1.2	1.2	1.3
Vesiculation	0.5	0.4	0.5	0.5
Crusting	0.6	0.7	0.8	0.8

HOW SUPPLIED: Fluticasone Propionate Cream, 0.05% is supplied in:

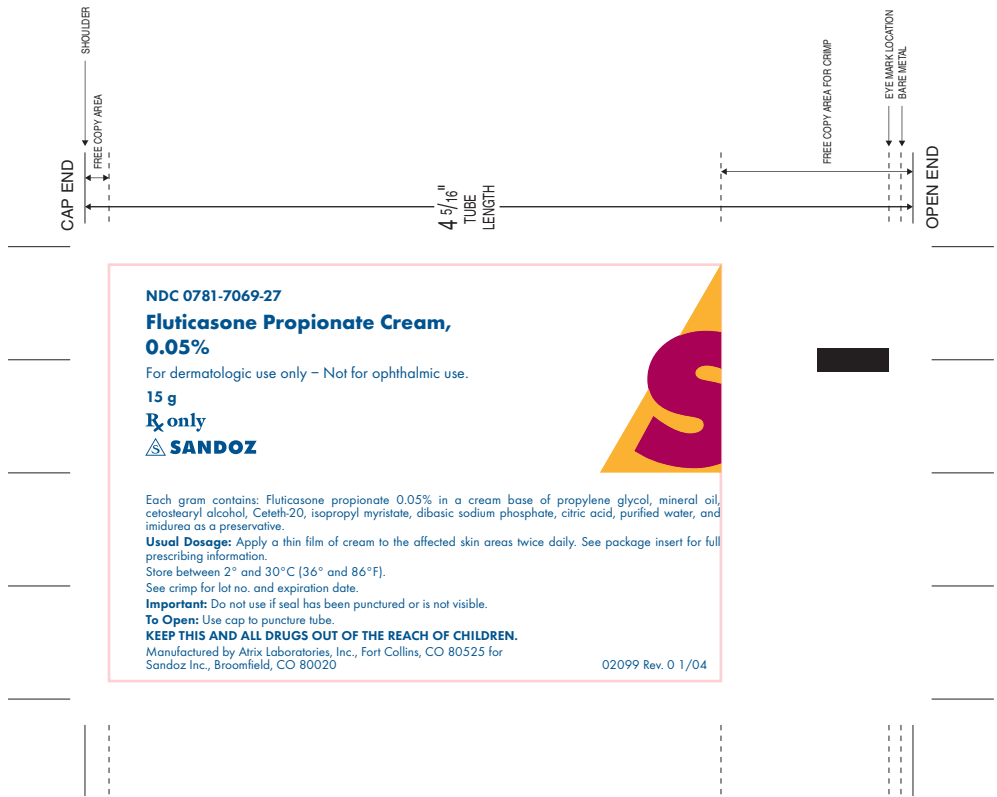
- 15 g tubes (NDC 0781-7069-27)
- 30 g tubes (NDC 0781-7069-03)
- 60 g tubes (NDC 0781-7069-35)

Store between 2° and 30°C (36° and 86°F).

Manufactured by:
Atrix Laboratories, Inc.
Fort Collins, CO 80525 for

Sandoz Inc.
Broomfield, CO 80020

04417 Rev. 0 1/04



NDC 0781-7069-27

**Fluticasone Propionate Cream,
0.05%**

For dermatologic use only – Not for ophthalmic use.

15 g

Rx only

SANDOZ



Each gram contains: Fluticasone propionate 0.05% in a cream base of propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as a preservative.

Usual Dosage: Apply a thin film of cream to the affected skin areas twice daily. See package insert for full prescribing information.

Store between 2° and 30°C (36° and 86°F).

See crimp for lot no. and expiration date.

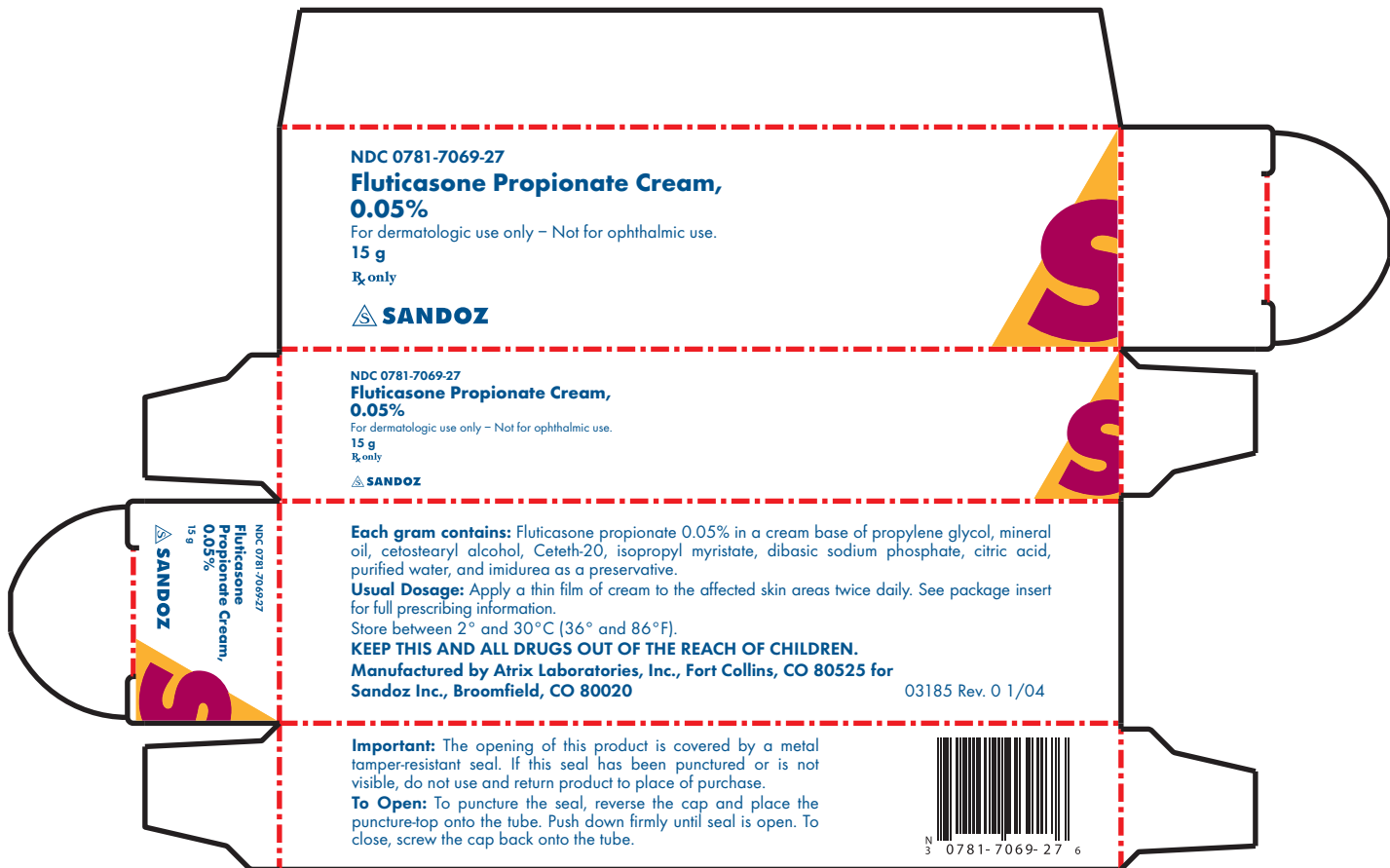
Important: Do not use if seal has been punctured or is not visible.

To Open: Use cap to puncture tube.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by Atrix Laboratories, Inc., Fort Collins, CO 80525 for Sandoz Inc., Broomfield, CO 80020

02099 Rev. 0 1/04



NDC 0781-7069-27
**Fluticasone Propionate Cream,
0.05%**

For dermatologic use only – Not for ophthalmic use.

15 g

Rx only



NDC 0781-7069-27
**Fluticasone Propionate Cream,
0.05%**

For dermatologic use only – Not for ophthalmic use.

15 g

Rx only



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Store between 2° and 30°C (36° and 86°F).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by Atrix Laboratories, Inc., Fort Collins, CO 80525 for

Sandoz Inc., Broomfield, CO 80020

03185 Rev. 0 1/04

Important: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.

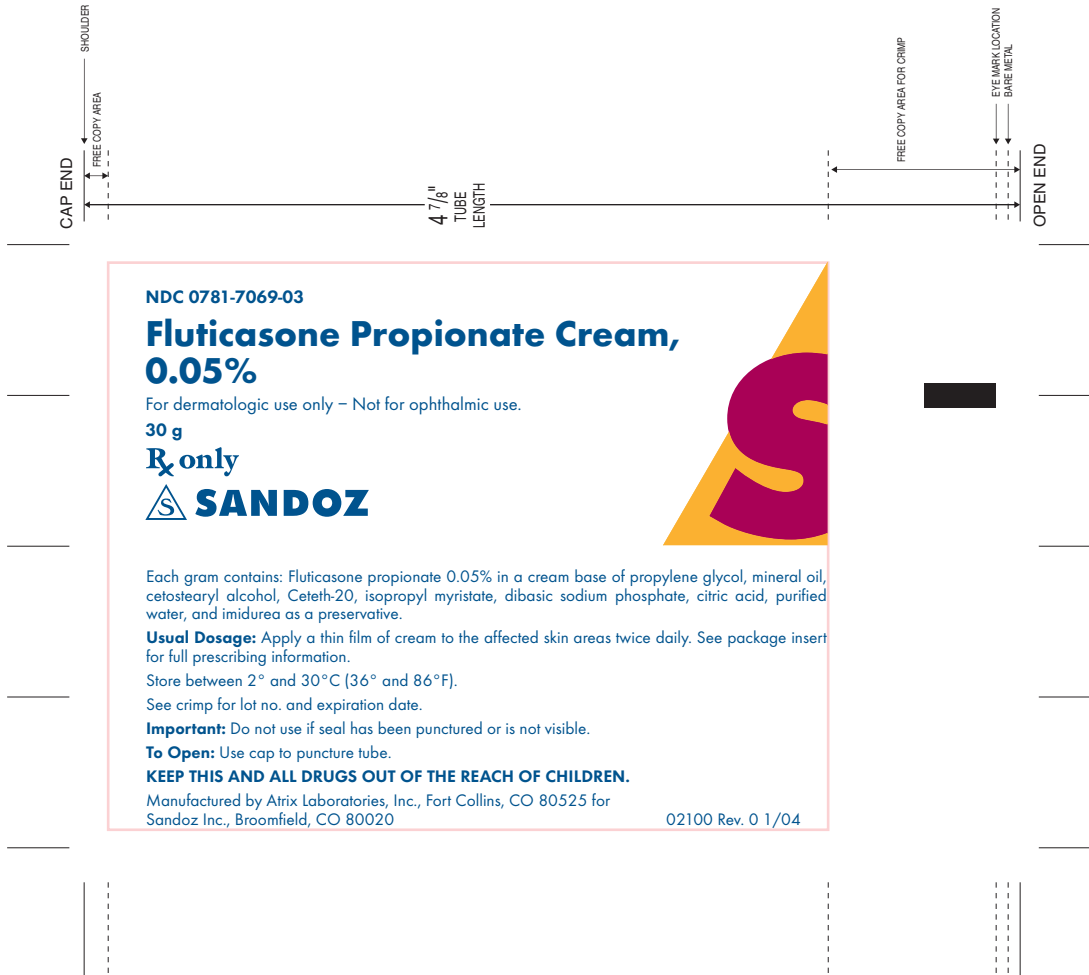
To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.



N
3 0781-7069-27 6

NDC 0781-7069-27
Fluticasone
Propionate Cream,
0.05%
15 g
SANDOZ





NDC 0781-7069-03

Fluticasone Propionate Cream, 0.05%

For dermatologic use only – Not for ophthalmic use.

30 g

Rx only

 **SANDOZ**

Each gram contains: Fluticasone propionate 0.05% in a cream base of propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as a preservative.

Usual Dosage: Apply a thin film of cream to the affected skin areas twice daily. See package insert for full prescribing information.

Store between 2° and 30°C (36° and 86°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 tube.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by Atrix Laboratories, Inc., Fort Collins, CO 80525 for Sandoz Inc., Broomfield, CO 80020

02100 Rev. 0 1/04

NDC 0781-7069-03

**Fluticasone Propionate Cream,
0.05%**

For dermatologic use only – Not for ophthalmic use.

30 g

Rx only



NDC 0781-7069-03

**Fluticasone Propionate Cream,
0.05%**

For dermatologic use only – Not for ophthalmic use.

30 g

Rx only



Each gram contains: Fluticasone propionate 0.05% in a cream base of propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as a preservative.

Usual Dosage: Apply a thin film of cream to the affected skin areas twice daily. See package insert for full prescribing information.

Store between 2° and 30°C (36° and 86°F).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

**Manufactured by Atrix Laboratories, Inc., Fort Collins, CO 80525 for
Sandoz Inc., Broomfield, CO 80020**

03186 Rev. 0 1/04

Important: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.

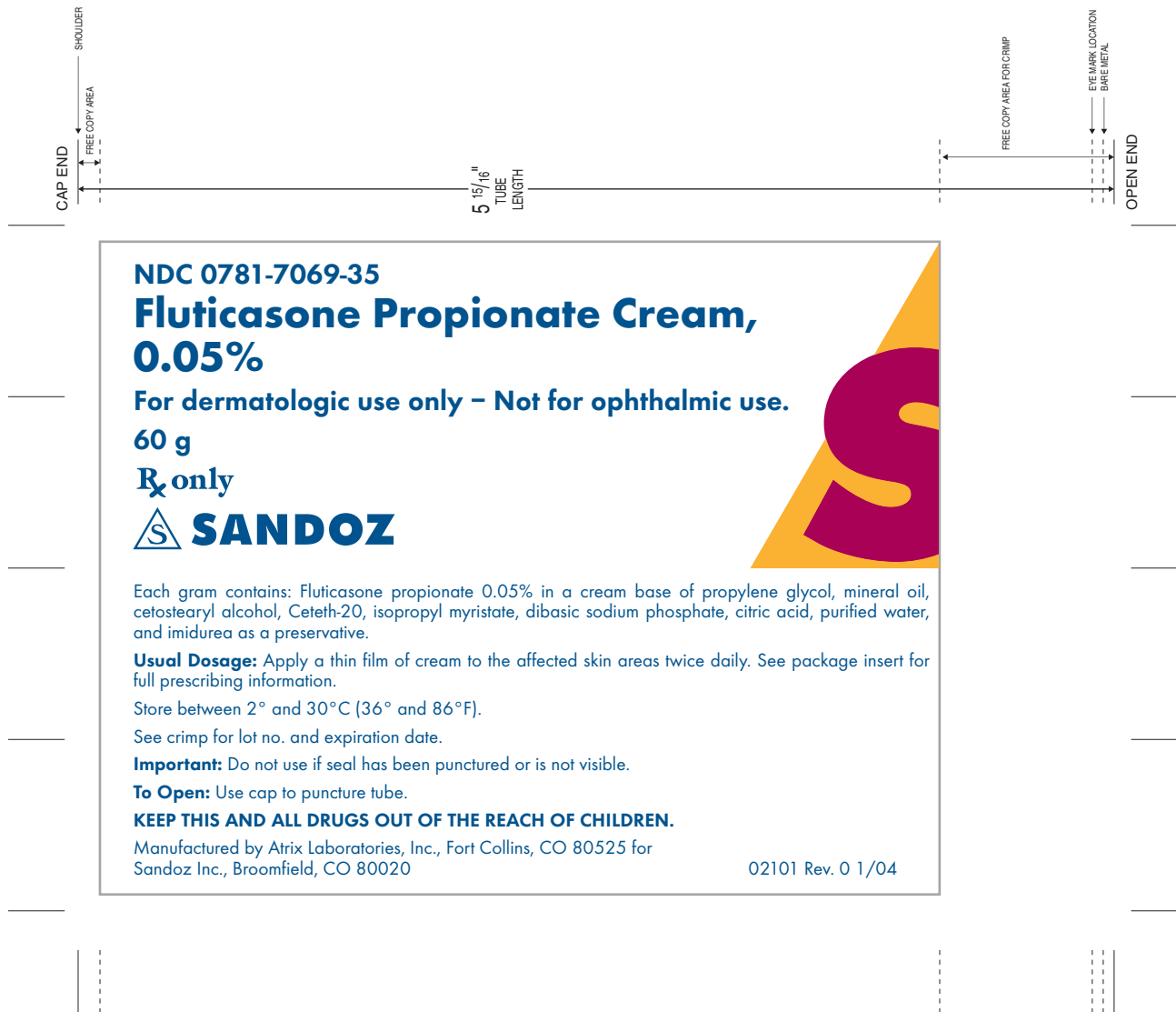
To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.



N 3 0781-7069-03 0

NDC 0781-7069-03
Fluticasone
Propionate Cream,
0.05%
30 g
SANDOZ





NDC 0781-7069-35

Fluticasone Propionate Cream, 0.05%

For dermatologic use only – Not for ophthalmic use.

60 g

R_x only



Each gram contains: Fluticasone propionate 0.05% in a cream base of propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as a preservative.

Usual Dosage: Apply a thin film of cream to the affected skin areas twice daily. See package insert for full prescribing information.

Store between 2° and 30°C (36° and 86°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 tube.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by Atrix Laboratories, Inc., Fort Collins, CO 80525 for Sandoz Inc., Broomfield, CO 80020

02101 Rev. 0 1/04

NDC 0781-7069-35

**Fluticasone Propionate Cream,
0.05%**

For dermatologic use only – Not for ophthalmic use.

60 g

Rx only



NDC 0781-7069-35

**Fluticasone Propionate Cream,
0.05%**

For dermatologic use only – Not for ophthalmic use.

60 g

Rx only



Each gram contains: Fluticasone propionate 0.05% in a cream base of propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as a preservative.

Usual Dosage: Apply a thin film of cream to the affected skin areas twice daily. See package insert for full prescribing information.

Store between 2° and 30°C (36° and 86°F).

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured by Atrix Laboratories, Inc., Fort Collins, CO 80525 for

Sandoz Inc., Broomfield, CO 80020

03187 Rev. 0 1/04

Important: The opening of this product is covered by a metal tamper-resistant seal. If this seal has been punctured or is not visible, do not use and return product to place of purchase.

To Open: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.



N 3 0781-7069-35 1

NDC 0781-7069-35
Fluticasone
Propionate Cream,
0.05%
60 g
SANDOZ



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-633

LABELING REVIEW(S)

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

ANDA Number:	76-633
Date of Submission:	December 31, 2002 (Original draft labeling)
Applicant's Name:	Atrix Laboratories, Inc.
Established Name:	Fluticasone Propionate Cream, 0.05%.
Proposed Proprietary Name:	N/A

Labeling Deficiencies:

1. GENERAL

Your proposed storage temperature statement "Store between 2°C and 30°C (36°F and 86°F)" is being reviewed by the chemistry team.

2. CONTAINER – 15 gram, 30 gram, 60 gram tubes.

Satisfactory in final printed labeling as of December 31, 2002 submission.

3. CARTON – 15 gram, 30 gram, 60 gram tubes.

Satisfactory in final printed labeling as of December 31, 2002 submission.

4. INSERT

a. **GENERAL**

Please follow the reference listed drug's table format by adding appropriate columns and rows to your tables throughout the labeling.

b. **PRECAUTIONS**

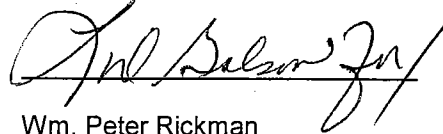
Geriatric Use: Please change "n" from — to 126 in the first sentence per last approved labeling of the reference listed drug.

Please revise your labels and labeling, as instructed above, and 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. We suggest that you routinely monitor the following website for any approved changes-

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

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



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

Attachment: Mocked-up copy the firm's draft labeling.

**APPEARS THIS WAY
ON ORIGINAL**

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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 26		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?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR]		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	
<i>LABELING</i>			
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	

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 (p. #) 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 p. # 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?[see FTR]		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.		X	
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. See FTR.			
--	--	--	--

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Cutivate Cream, 0.05% (NDA 19-958/S-013) approved on April 16, 2002.

2. PATENTS/EXCLUSIVITIES

Patent Data

Ap pl No	Prod No	Patent No	Patent Expiration	Use Code
019958	001	4335121	NOV 14,2003	
019958	001	4335121*PED	MAY 14,2004	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor has filed a Paragraph III Certification on this patent and the sponsor's statement is correct. [See Vol 1.1. page 6-7]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Atrix Laboratories, Inc.
701 Centre Avenue
Fort Collins, CO 80526

[See Vol 1.1. page 106]

4. CONTAINER/CLOSURE: [Vol 1.1. page 263]

Component	Mfr/DMF	Liner	End Sealant	Resin	Colorant
15 gram Aluminum Tube	_____	_____	N/A		
Cap (Atrix P/N 02070)	DMF # _____	_____		_____	_____
30 gram Aluminum tube	_____	_____	N/A		
Cap (Atrix P/N 02071)	DMF # _____	_____		_____	_____
60 gram Aluminum tube	_____	_____	_____		
Cap (Atrix P/N 02074)	DMF# _____			_____	_____ White

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement and identical to the reference listed drug. [Vol. 1.1. page 40-43]

6. PACKAGING CONFIGURATIONS

RLD: 15 gram, 30 gram, and 60 gram tubes.
ANDA: 15 gram, 30 gram, and 60 gram tubes. Tubes are aluminum and the caps are made of _____ resin, and the tubes will be packaged in a printed chipboard carton.

[See Vol. 1.1. page 262]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None
RLD: Store between 2°C and 30°C (36°F and 86°F)
ANDA: Store between 2°C and 30°C (36°F and 86°F)

The chemistry review is completed and the sponsor was asked to provide additional stability study to justify the recommended storage condition. To avoid any confusion to the sponsor, I am not making any comments regarding the storage temperature recommendation at this time.
[See attached chemistry review, comment section]

8. FINISHED DOSAGE FORM

White to off-white uniform smooth cream.
[See Vol 1.1. page 305-310]

Date of Review: 7/31/03

Date of Submission: 12/31/03

Primary Reviewer: Melaine Shin Date: _____

Team Leader: John Grace Date: 9/5/2007

cc:
ANDA: 76-633
DUP/DIVISION FILE
HFD-613/MShin/JGrace (no cc)
v:\firmsam\Atrx\ltrs&rev\76633NA1.Labeling.doc
Review

7 pages of draft labeling
have been removed
from this portion of the
document.

APPROVAL SUMMARY

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

ANDA Number: 76-633

Date of Submission: February 3, 2004

Applicant's Name: Atrix Laboratories, Inc.

Established Name: Fluticasone Propionate Cream, 0.05%.

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

- Do you have 12 Final Printed Labels and Labeling? Yes
- Container Labels: (15 g, 30 g, 60 g) – Satisfactory in FPL as of February 3, 2004 EDR submission located in the PDF FILES. [Revise 01/04; Code #s 02099, 02100 and 02101, respectively]
- Carton Labeling: (15 g, 30 g, 60 g) – Satisfactory in FPL as of February 3, 2004 EDR submission located in the PDF FILES.
[Revise 01/04; Code #s 02099, 02100 and 02101, respectively. 03185, 03186 and 03187]
- Professional Package Insert Labeling: Satisfactory in FPL as of February 3, 2004 EDR submission located in the PDF FILES. [Revise 01/04; Code # 04417]
- **COMMENT: NET PATH for ANDA 76-633 : \\CDSESUBOGD1\N76633\N 000\2004-02-03 -Final printed Labels and labeling LOCATED IN PDF FILES**

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Cutivate® Cream
- NDA Number: 19-958/S-013
- NDA Drug Name: Fluticasone propionate cream, 0.05%
- NDA Firm: Glaxo Wellcome Inc.
- Date of Approval of NDA Insert: April 16, 2002
- 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
- Revisions needed post-approval: No
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 19-958

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4335121	November 14, 2003	None	None	Paragraph III	Same as
43351221* Peds	May 14, 2004			Paragraph III	Same as

Exclusivity Data– NDA 19-958

Code	Reference	Expiration	Labeling Impact
	There is no unexpired exclusivity for this product.		

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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 26		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?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
<i>PACKAGING</i> -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR]		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	
<i>LABELING</i>			
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	
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 (p. #) 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 p. # 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?[see FTR]		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.		X	
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. See FTR.			

FOR THE RECORD:

1. MODEL LABELING: The review was base on Cutivate Cream® (NDA 19-958/S-013) approved on April 16, 2002. Supplement (S-013) added a Geriatric Use subsection to the PRECAUTIONS and DOSAGE and ADMINSTRATION sections of the labeling.

2. PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019958	001	4335121	NOV 14,2003	
019958	001	4335121*PED	MAY 14,2004	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor has filed a Paragraph III Certification on these patents and the sponsor's statement is correct. [See Vol 1.1. page 6-7]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Atrix Laboratories, Inc.
701 Centre Avenue
Fort Collins, CO 80526
[See Vol 1.1. page 106]

4. CONTAINER/CLOSURE: [Vol 1.1. page 263]

The drug product will be packaged in a aluminum tube with _____ and a white — cap in the sizes of 15 g, 30 g and 60 g fills

5. INACTIVE INGREDIENTS - The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement and identical to the reference listed drug. [Vol. 1.1. page 40-43]

6. PACKAGING CONFIGURATIONS

- RLD: 15 gram, 30 gram, and 60 gram tubes.
- ANDA: 15 gram, 30 gram, and 60 gram tubes. Tubes are aluminum and the caps are made of _____ resin, and the tubes will be packaged in a printed chipboard carton. [See Vol. 1.1. page 262]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: None
- RLD: Store between 2°C and 30°C (36F° and 86°F)
- ANDA: Store between 2°C and 30°C (36F° and 86°F)

8. FINISHED DOSAGE FORM

White to off-white uniform smooth cream. [See Vol 1.1. page 305-310]

Date of Review:

Date of Submission: February 3, 2004

Primary Reviewer: B. Weitzman

Date: 3/24/2004

Team Leader: 

Date: 3/24/04

cc:

ANDA: 76-633 – EDR (PDF FILES) \\CDSE\SUBOGD1\N76633\N_000\2004-02-03
DUP/DIVISION FILE
HFD-613/BWeitzman/JGrace (no cc)
v:\firmsam\Atrix\ltrs&rev\76633EDRAP.Labeling.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-633

CHEMISTRY REVIEW(S)

ANDA 76-633

Fluticasone Propionate Cream, 0.05%

Atrix Laboratories, Inc.

**Benjamin Lim, Ph.D.
Chemistry Division I**

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**APPEARS THIS WAY
ON ORIGINAL**



Chemistry Review Data Sheet

1. ANDA 76-633
2. REVIEW #: 1
3. REVIEW DATE: May 30, 2003
4. REVIEWER: Benjamin Lim, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date**Firm:**

Original Submission
Amendment (labeling and cGMP letters)
Patent Amendment
New Correspondence

December 31, 2002
February 24, 2003
February 26, 2003
April 17, 2003

Agency:

Acknowledgement Letter
(Acceptable for Filing: January 2, 2003)

February 26, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Atrix Laboratories, Inc.
Address: 2579 Midpoint Drive
Fort Collins, CO 80525-4417
Representative: Cheri Jones
Telephone: (970) 212-4901



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fluticasone Propionate Cream, 0.05%

9. LEGAL BASIS FOR SUBMISSION:

- a. The basis for Atrix Laboratories, Inc. proposed ANDA for Fluticasone Propionate Cream, 0.05% is the approved, referenced listed drug, Cutivate (Fluticasone Propionate) Cream, 0.05% of NDA #19-958 (Approved on December 18 1990), held by Glaxo Smith Kline.
- b. Atrix Laboratories, Inc. certifies, in accordance with Section 505(j)(2)(A)(vii)(III) of Title 1 of the FD&C Act as amended September 24, 1984, that United State Patent 4,335,121 by Glaxo Smith Kline will expire on November 14, 2003. Atrix Laboratories, Inc. does not intend to market this product prior to the expiry.

Note: Atrix submitted an amendment (dated 02/26/03) to revise the Patent Certification. Due to the pediatric exclusivity received by Glaxo Smith Kline, the patent 4,335,121, will expire on May 14, 2004.

10. PHARMACOL. CATEGORY:

The relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 0.05%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

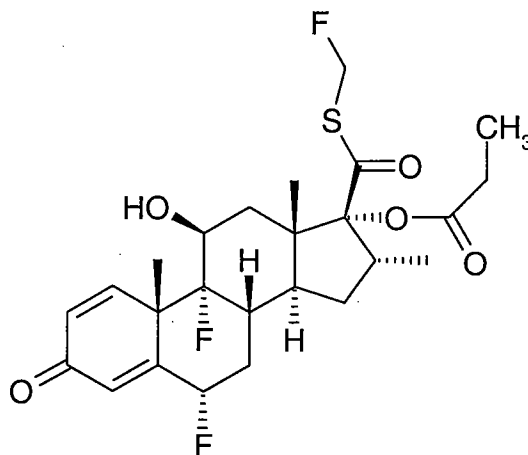
Not a SPOTS product

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

Cutivate; Fluticasone propionate; S-fluoromethyl-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxandrosta-1,4-diene-17 β -carbothioate;

Chemistry Review Data Sheet

Molecular Formula: $C_{25}H_{31}F_3O_5S$
 Molecular Weight: 500.5721
 CAS RN: 80474-14-2


17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	II	1	1	1	Inadequate	5/30/03	Reviewed by this reviewer B. Lim, Ph.D.
2	III	2	2	4			
3	III	3	3	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)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	3/10/03	J. D'Ambrogio (HFD-322)
Methods Validation	Not sending at this time		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

**APPEARS THIS WAY
ON ORIGINAL**



The Chemistry Review for ANDA 76-633

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable (Minor)

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)

Drug Substance

Fluticasone propionate is not an USP compendial item. Fluticasone propionate has a molecular weight of 500.6. It is a white to off-white powder and is insoluble in water, freely soluble in dimethylformamide, sparingly soluble in acetone and in dichloromethane; slightly soluble in ethanol (96%). It displays specific optical rotation between +32° and +36° (0.5% w/v in dichloromethane, t = 25°C and 589.3 nm).

Drug Product

Fluticasone Propionate Cream, 0.05% is not a USP compendial item. Atrix[®] Fluticasone Propionate Cream, 0.05% is white to off-white uniform smooth cream and has pH range of 5.0 and 6.1. The inactive ingredients are propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as a preservative. The drug product is packaged in white aluminum with _____ tube with white _____, cap in the sizes of 15 g, 30 g and 60 g tubes.

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. Corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins.

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

Topical administration for the treatments of relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.



Executive Summary Section

B. Basis for Approvability or Not-Approval Recommendation

Not approvable due to CMC deficiencies concerning raw materials, in-process, product release and stability specifications. The bioequivalence and labeling reviews are pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Benjamin Lim, Ph.D./06/09/03

S. Liu, Ph.D./06/09/03

W. Pamphile, Pharm.D./

Ben Lim 6/11/03
S.H. Liu 6/11/03
WP 6/11/03

C. CC Block

**APPEARS THIS WAY
ON ORIGINAL**

Redacted 19 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW # 1



Chemistry Assessment Section

- b. Please provide the pH specification.
 - c. The test and specifications presented on the regulatory stability protocol (p. 506) and regulatory shelf-life specifications (p. 507) are different. Please clarify.
11. The "alternate accelerated" condition is not acceptable as an accelerated stability study condition. The expiration dating will be based on the full term room temperature stability study data. Please provide the full term room temperature stability study data.
 12. Please provide additional stability study to justify the labeling storage conditions (2° - 30°C).
- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. The bioequivalence portion of your submission is under review. Deficiencies, if any, will be communicated to you under separate cover.
 2. The labeling portion of your submission is under review. Deficiencies, if any, will be communicated to you under separate cover.
 3. We will issue a method validation request to an FDA laboratory, when all testing issues are resolved. Please commit to work with the Agency to expeditiously resolve any deficiencies from the method validation study if the ANDA is approved prior to its completion.
 4. The firms referenced in your application must be in compliance with cGMP at the time of approval.
 5. Please provide any available drug product room temperature stability data.

Sincerely yours,

Rashmikant M. Patel 6/29/03

Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-633
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D./ *BL* 6/11/03
HFD-620/S. Liu, Ph.D./ *S.H. Liu* 6/11/03
HFD-617/W. Pamphile, Pharm.D./ *WP* 6/11/03

F/T by /

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TYPE OF LETTER: NOT APPROVABLE - MINOR

**APPEARS THIS WAY
ON ORIGINAL**

#2
ANDA 76-633

Fluticasone Propionate Cream, 0.05%

Atrix Laboratories, Inc.

**Benjamin Lim, Ph.D.
Chemistry Division I**

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**APPEARS THIS WAY
ON ORIGINAL**



Chemistry Review Data Sheet

1. ANDA 76-633
2. REVIEW #: 2
3. REVIEW DATE: November 10, 2003
4. REVIEWER: Benjamin Lim, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date**Firm:**

Original Submission
Amendment (labeling and cGMP letters)
Patent Amendment
New Correspondence

December 31, 2002
February 24, 2003
February 26, 2003
April 17, 2003

Agency:

Acknowledgement Letter
(Acceptable for Filing: January 2, 2003)
CMC Deficiency Letter

February 26, 2003
June 24, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

New Correspondence
Minor Amendment
Amendment

July 28, 2003
October 6, 2003
December 5, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Atrix Laboratories, Inc.
Address: 2579 Midpoint Drive
Fort Collins, CO 80525-4417
Representative: Cheri Jones



CHEMISTRY REVIEW



Chemistry Assessment Section

Telephone / Fax: (970) 212-4901 / (970) 482-9734

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Fluticasone Propionate Cream, 0.05%

9. LEGAL BASIS FOR SUBMISSION: See Review #1

10. PHARMACOL. CATEGORY:

The relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 0.05%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

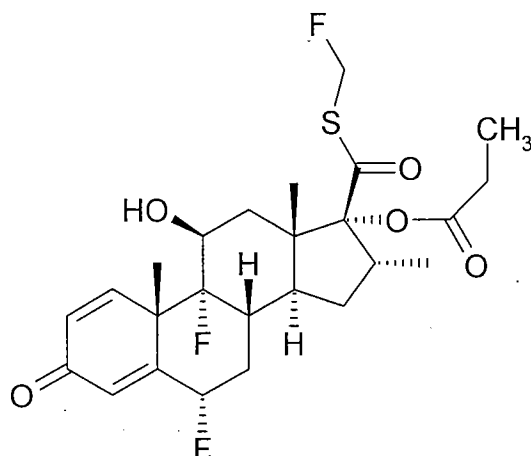
Not a SPOTS product

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

Cutivate; Fluticasone propionate; S-fluoromethyl-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate;

Molecular Formula: C₂₅H₃₁F₃O₅S
Molecular Weight: 500.5721
CAS RN: 80474-14-2

Chemistry Assessment Section


17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Inadequate	1/30/04	Reviewed by this reviewer B. Lim, Ph.D.
	III			4			
	III			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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		



CHEMISTRY REVIEW



Chemistry Assessment Section

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	3/10/03	J. D'Ambrogio (HFD-322)
Methods Validation	See Item 31		
Labeling	Pending		
Bioequivalence	Acceptable	1/22/04	M. Makary
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

Note: The Section B of the last NA letter has been acknowledged by the applicant.

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA 76-633

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable (Minor)

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)

Drug Substance

Fluticasone propionate is not an USP compendial item. Fluticasone propionate has a molecular weight of 500.6. It is a white to off-white powder and is insoluble in water, freely soluble in dimethylformamide, sparingly soluble in acetone and in dichloromethane; slightly soluble in ethanol (96%). It displays specific optical rotation between +32° and +36° (0.5% w/v in dichloromethane, t = 25°C and 589.3 nm).

Drug Product

Fluticasone Propionate Cream, 0.05% is not a USP compendial item. Atrix's Fluticasone Propionate Cream, 0.05% is white to off-white uniform smooth cream and has pH range of 5.0 and 6.1. The inactive ingredients are propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as a preservative. The drug product is packaged in white aluminum with _____ tube with white _____ cap in the sizes of 15 g, 30 g and 60 g tubes.

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. Corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins.

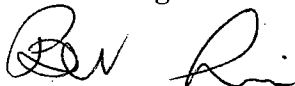
B. Description of How the Drug Product is Intended to be Used

Topical administration for the treatments of relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Executive Summary Section

B. Basis for Approvability or Not-Approval Recommendation

Not approvable due to CMC deficiencies concerning raw materials, product release and stability specifications. The labeling review is pending.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Benjamin Lim, Ph.D./11/10/03

S. Liu, Ph.D./ *S.H. Liu* 2/2/04

W. Pamphile, Pharm.D./ *WP* 2/2/04

Ben Lim 2/2/04

C. CC Block

**APPEARS THIS WAY
ON ORIGINAL**

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information from

CHEMISTRY REVIEW # 2



CHEMISTRY REVIEW



Chemistry Assessment Section

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-633

APPLICANT: Atrix Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Cream, 0.05%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (DMF) No. — remains inadequate. The DMF holder has been notified. Please do not respond to this letter until you have been informed by the DMF holder that all deficiencies have been addressed.

2.

3.

4.

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

Please provide any available drug product room temperature stability data.

Sincerely yours,

Rashmikant M. Patel for 2/2/04

Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research



CHEMISTRY REVIEW



Chemistry Assessment Section

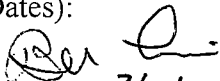
cc: ANDA 76-633
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D./

HFD-620/S. Liu, Ph.D./

HFD-617/W. Pamphile, Pharm.D./ ~~wp~~ 2/2/04


S.H. Liu 2/2/04

2/2/04

F/T by / wp

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TYPE OF LETTER: NOT APPROVABLE - MINOR

**APPEARS THIS WAY
ON ORIGINAL**

#3
ANDA 76-633

Fluticasone Propionate Cream, 0.05%

Atrix Laboratories, Inc.

**Benjamin Lim, Ph.D.
Chemistry Division I**

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23. RAW MATERIAL CONTROLS	12
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B. Inactive Ingredients.....	13
24. OTHER FIRM(s)	13
25. MANUFACTURING AND PROCESSING	13
26. CONTAINER	13
27. PACKAGING AND LABELING	13
28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM).....	13



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30. MICROBIOLOGY14

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32. LABELING.....15

33. ESTABLISHMENT INSPECTION15

34. BIOEQUIVALENCE15

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL
EXCLUSION:.....15

**APPEARS THIS WAY
ON ORIGINAL**



Chemistry Review Data Sheet

1. ANDA 76-633
2. REVIEW #: 3
3. REVIEW DATE: April 16, 2004
4. REVIEWER: Benjamin Lim, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date**Firm:**

Original Submission	December 31, 2002
Amendment (labeling and cGMP letters)	February 24, 2003
Patent Amendment	February 26, 2003
New Correspondence	April 17, 2003
New Correspondence	July 28, 2003
Minor Amendment	October 6, 2003
Amendment	December 5, 2003

Agency:

Acknowledgement Letter (Acceptable for Filing: January 2, 2003)	February 26, 2003
CMC Deficiency Letter	June 24, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Unsolicited Minor Amendment	February 3, 2004
CMC Deficiency Letter #2	February 4, 2004
Minor Amendment	February 19, 2004
Minor Amendment	March 10, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Atrix Laboratories, Inc.



CHEMISTRY REVIEW



Chemistry Assessment Section

Address: 2579 Midpoint Drive
Fort Collins, CO 80525-4417

Representative: Cheri Jones

Telephone / Fax: (970) 212-4901 / (970) 482-9734

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): Fluticasone Propionate Cream, 0.05%

9. LEGAL BASIS FOR SUBMISSION: See Review #1

10. PHARMACOL. CATEGORY:

The relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 0.05%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

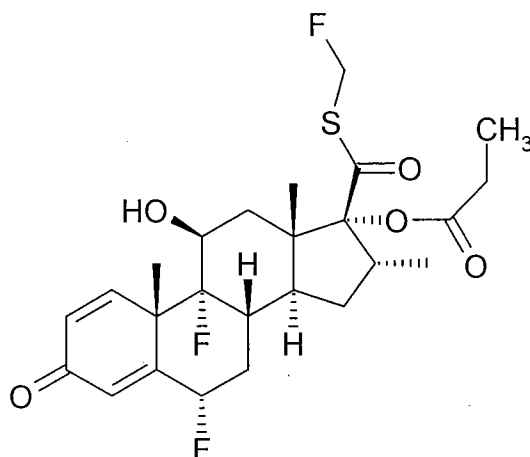
Not a SPOTS product

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

Cutivate; Fluticasone propionate; S-fluoromethyl-6alpha,9alpha-difluoro-11beta-hydroxy-16alpha-methyl-3-oxo-17alpha-propionyloxyandrosta-1,4-diene-17beta-carbothioate;

Molecular Formula: $C_{25}H_{31}F_3O_5S$
Molecular Weight: 500.5721
CAS RN: 80474-14-2

Chemistry Assessment Section



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Adequate	4/16/04	Reviewed by this reviewer B. Lim, Ph.D.
	III			4			
	III			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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		



CHEMISTRY REVIEW



Chemistry Assessment Section

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	3/10/03	J. D'Ambrogio (HFD-322)
Methods Validation	See Item 31		
Labeling	Acceptable	3/24/2004	B. Weitzman
Bioequivalence	Acceptable	1/22/04	M. Makary
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA 76-633

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

Fluticasone propionate is not a USP compendial item. Fluticasone propionate has a molecular weight of 500.6. It is a white to off-white powder and is insoluble in water, freely soluble in dimethylformamide, sparingly soluble in acetone and in dichloromethane; slightly soluble in ethanol (96%). It displays specific optical rotation between $+32^\circ$ and $+36^\circ$ (0.5% w/v in dichloromethane, $t = 25^\circ\text{C}$ and 589.3 nm).

Drug Product

Fluticasone Propionate Cream, 0.05% is not a USP compendial item. Atrix's Fluticasone Propionate Cream, 0.05% is white to off-white uniform smooth cream and has pH range of 5.0 and 6.1. The inactive ingredients are propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as a preservative. The drug product is packaged in white aluminum with _____ tube with white _____ cap in the sizes of 15 g, 30 g, and 60 g tubes.

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. Corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins.

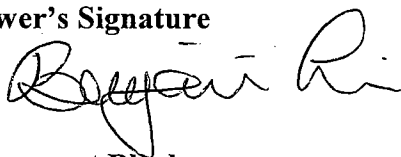
B. Description of How the Drug Product is Intended to be Used

Topical administration for the treatments of relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Executive Summary Section

B. Basis for Approvability or Not-Approval Recommendation


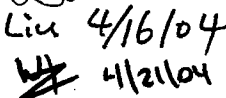
There are no CMC deficiencies at this time. The Bioequivalence, labeling and EES are all acceptable.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Benjamin Lim, Ph.D./

S. Liu, Ph.D./

W. Pamphile, Pharm.D./


S.H. Liu 4/16/04
 4/21/04

4/16/04

C. CC Block

**APPEARS THIS WAY
ON ORIGINAL**

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confidential commercial

information from

CHEMISTRY REVIEW #3



31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS

The method validation will not be requested based on the current OGD guidelines.

32. LABELING Acceptable on March 24, 2004 by B. Weitzman.

33. ESTABLIS-MENT INSPECTION

Acceptable on March 10, 2003 by J. D'Ambrogio (HFD-322)

34. BIOEQUIVALENCE Acceptable on January 22, 2004 by M. Makary

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Satisfactory in review #1

**APPEARS THIS WAY
ON ORIGINAL**



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-633
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D./

HFD-620/S. Liu, Ph.D./

HFD-617/W. Pamphile, Pharm.D./

B. Lim 4/16/04
S. H. Liu 4/21/04
W. Pamphile 4/21/04

F/T by

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TYPE OF LETTER: APPROVABLE

**APPEARS THIS WAY
ON ORIGINAL**

ANDA 76-633

Fluticasone Propionate Cream, 0.05%

Atrix Laboratories, Inc.

**Benjamin Lim, Ph.D.
Chemistry Division I**

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B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation	9
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Chemistry Assessment	10
20. COMPONENTS AND COMPOSITION	10
21. FACILITIES	10
22. SYNTHESIS	10
23. RAW MATERIAL CONTROLS	11
A. Drug Substance(s)	11
B. Inactive Ingredients.....	11
24. OTHER FIRM(s)	12
25. MANUFACTURING AND PROCESSING	12
26. CONTAINER	12
27. PACKAGING AND LABELING	12
28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM).....	12



29. STABILITY.....12

30. MICROBIOLOGY13

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS13

32. LABELING.....13

33. ESTABLISHMENT INSPECTION13

34. BIOEQUIVALENCE13

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL
EXCLUSION:.....13

APPEARS THIS WAY
ON ORIGINAL



Chemistry Review Data Sheet

1. ANDA 76-633
2. REVIEW #: 4
3. REVIEW DATE: May 4, 2004
4. REVIEWER: Benjamin Lim, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date**Firm:**

Original Submission	December 31, 2002
Amendment (labeling and cGMP letters)	February 24, 2003
Patent Amendment	February 26, 2003
New Correspondence	April 17, 2003
New Correspondence	July 28, 2003
Minor Amendment	October 6, 2003
Amendment	December 5, 2003
Unsolicited Minor Amendment	February 3, 2004
Minor Amendment	February 19, 2004
Minor Amendment	March 10, 2004

Agency:

Acknowledgement Letter (Acceptable for Filing: January 2, 2003)	February 26, 2003
CMC Deficiency Letter	June 24, 2003
CMC Deficiency Letter #2	February 4, 2004
Telephone call from Dr. Patel	April 22, 2004
Tentative Approval Letter	April 26, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Minor Amendment	April 22, 2004
Minor Amendment	April 27, 2004



CHEMISTRY REVIEW



Chemistry Assessment Section

7. NAME & ADDRESS OF APPLICANT:

Name: Atrix Laboratories, Inc.
Address: 2579 Midpoint Drive
Fort Collins, CO 80525-4417
Representative: Cheri Jones
Telephone / Fax: (970) 212-4901 / (970) 482-9734

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fluticasone Propionate Cream, 0.05%

9. LEGAL BASIS FOR SUBMISSION: See Review #1

10. PHARMACOL. CATEGORY:

The relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 0.05%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

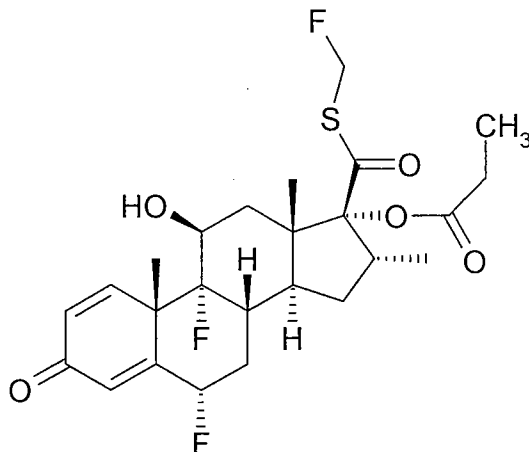
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Cutivate; Fluticasone propionate; S-fluoromethyl-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -propionyloxyandrosta-1,4-diene-17 β -carbothioate;

Molecular Formula: C₂₅H₃₁F₃O₅S

Chemistry Assessment Section

Molecular Weight: 500.5721
 CAS RN: 80474-14-2



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Adequate	4/16/04	Reviewed by this reviewer B. Lim, Ph.D.
	III			4			
	III			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:



CHEMISTRY REVIEW



Chemistry Assessment Section

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	3/10/03	J. D'Ambrogio (HFD-322)
Methods Validation	See Item 31		
Labeling	Acceptable	3/24/2004	B. Weitzman
Bioequivalence	Acceptable	1/22/04	M. Makary
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

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

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA 76-633

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is recommended for final approval

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)

Drug Substance

Fluticasone propionate is not a USP compendial item. Fluticasone propionate has a molecular weight of 500.6. It is a white to off-white powder and is insoluble in water, freely soluble in dimethylformamide, sparingly soluble in acetone and in dichloromethane; slightly soluble in ethanol (96%). It displays specific optical rotation between $+32^\circ$ and $+36^\circ$ (0.5% w/v in dichloromethane, $t = 25^\circ\text{C}$ and 589.3 nm).

Drug Product

Fluticasone Propionate Cream, 0.05% is not a USP compendial item. Atrix's Fluticasone Propionate Cream, 0.05% is white to off-white uniform smooth cream and has pH range of 5.0 and 6.1. The inactive ingredients are propylene glycol, mineral oil, cetostearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as a preservative. The drug product is packaged in white aluminum with _____ tube with white _____ cap in the sizes of 15 g, 30 g, and 60 g tubes.

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. Corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins.

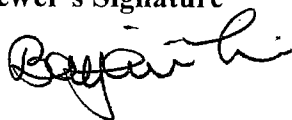
B. Description of How the Drug Product is Intended to be Used

Topical administration for the treatments of relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Executive Summary Section

B. Basis for Approvability or Not-Approval Recommendation

CMC, bioequivalence, labeling, and EES are all acceptable.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Benjamin Lim, Ph.D./

S. Liu, Ph.D./

W. Pamphile, Pharm.D./

Bu L 5/10/04

S.H. Liu 5/10/04

~~*W*~~ 5/10/04

C. CC Block

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ON ORIGINAL**

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #4



CHEMISTRY REVIEW



Chemistry Assessment Section

cc: ANDA 76-633
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D./

HFD-620/S. Liu, Ph.D./

HFD-617/W. Pamphile, Pharm.D./

Ban Li 5/10/04

S. H. Liu 5/10/04

WP 5/10/04

F/T by

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TYPE OF LETTER: APPROVABLE

**APPEARS THIS WAY
ON ORIGINAL**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-633

BIOEQUIVALENCE REVIEW(S)

Fluticasone propionate Cream
0.05%
ANDA #76-633
Reviewer: Moheb H. Makary
W. 76633N1202.doc

Atrix Laboratories, Inc.
Fort Collins, Co.
Submission date:
December 31, 2002

Review of a Pilot Dose Response Study and a Pharmacodynamic
Bioequivalence Study

Executive Summary

This submission consisted of a pilot dose-response study on the designated RLD (Cutivate® Cream 0.05%) and a pivotal bioequivalence study. For the pilot study, based on a population fitting of the chromaMeter dose-response data, an ED₅₀ of approximately 60 minutes was calculated. For the pivotal bioequivalence study, the firm used D₁, ED₅₀ and D₂ values of 30, 60 and 120 minutes, respectively. The selection of these values was appropriate. The 90% confidence intervals comparing the test and reference products were within the acceptable limit of 80-125%.

However, the application was found incomplete since the firm used occlusion in both the pilot and the pivotal studies, without submitting the evidence that the reference product did not provide measurable vasoconstrictor response without occlusion.

Introduction

Atrix Laboratories Inc. is seeking approval to market its fluticasone propionate cream 0.05%, and has submitted pilot dose-response and pivotal *in vivo* vasoconstriction bioequivalence studies for the corticosteroid component.

Type of Submission: Original ANDA

Reference Listed Drug: Cutivate^R Cream, 0.05% (NDA #19958, December 18, 1990; manufactured by GlaxoSmithKline.

Background

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. Cutivate^R cream is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

History of Submissions

The DBE has reviewed only two protocols (control #s? _____, dated 6/11/02) on Fluticasone Propionate Cream, 0.05%. The DBE has not reviewed any submissions on Fluticasone Propionate Cream, 0.05% or Fluticasone Propionate Ointment, 0.005%.

A. Pilot Study – Dose-Response Study of Fluticasone Propionate Cream 0.05% (Vasoconstrictor Assay: Study No. 10100003)

Objective

To determine the dose-response relationship for Cutivate^R (fluticasone propionate) cream, 0.05% to be used to estimate the ED₅₀ of D1 and D2 parameters for use in a full bioequivalence study. The dose response study was based on the vasoconstrictor assay.

Study No: 10100003

Applicant: Atrix Laboratories, Inc.

Study site: _____

Principal Investigator: _____, M.D., _____

Study date: 12/22/01

Study design: One-period randomized design.

Subjects Fifteen (15) subjects who were chosen for participation in this study were healthy, asymptomatic, non-tobacco-users (for 30 days prior to dosing), females in the age range of 19 to 47 years. They were within 20% of their ideal weight as specified in the protocol.

Screening of Subjects

Potential study participants were screened to determine blanching response to Cutivate^R (fluticasone propionate cream) 0.05% cream. A 10-microliter application of the cream was applied to the upper arm (above the forearm) and left in place for 3 hours (± 15 minutes) under occluded conditions. The site was evaluated visually approximately 6-9 hours after application. All subjects were selected based on a demonstrated blanching response, and the absence of any clinically significant findings on the medical history or clinical assessment. Selected subjects had no history of allergy or hypersensitivity to any corticosteroids or to any topical products. They had no skin condition or coloration, which would interfere with the assessment of skin blanching. All subjects tested negative on the urine pregnancy test and drug screen.

Drug product: Cutivate^R (fluticasone propionate cream) 0.05% cream, Lot #1C299, Expiration Date 03/04.

Randomization: Cutivate^R (fluticasone propionate cream) 0.05% cream was applied to 8 designated sites on both arms as determined

by the randomization schedule. Two untreated reference sites were also randomly assigned on each arm.

Preparation

The arms of each subject were washed with a mild soap (Liquid Neutrogena Facial Cleansing Formula) and gently dried within approximately 2 hours prior to dosing.

Staggered Application and Synchronized Removal of the Drug Product

Ten (10) circular (approximately 1.6 cm diameter) application sites were designated on the flexor surface of each forearm between the wrist and the elbow. The sites were marked with numbers 1-10 on the right arm from wrist to elbow and 11-20 on the left arm from wrist to elbow for ease of identification. Care was taken that sites were not placed within 3 cm of the wrist or antecubital fossa. The washers were no closer than 2 cm apart center-to-center.

After baseline ChromaMeter readings, an open washer was positioned over each site and taped to the forearm using hypoallergenic paper tape on the sides of the washer so that the treated area was not occluded. Using a _____-ul glass _____, a 10 microliter application of Cutivate^R (fluticasone propionate cream) 0.05% cream was applied to 8 assigned sites on each arm at times according to the randomization schedule. Immediately after dosing, a piece of hypoallergenic paper tape was placed over the open area of the washer to occlude the site. The untreated sites were also occluded. Two sites on each arm were left untreated.

Cutivate^R (fluticasone propionate cream) 0.05% cream was applied to both arms at 0.05, 0.25, 0.5, 1, 2, 3, 4 and 6 hours prior to removal. The applications were spread evenly over the skin surface at each site with the conical tip of a 1.5 mL _____ microcentrifuge tube.

**Assessment of
Blanching**

Synchronized Removal: All applications on each participant's arm were removed at the same time point (0 hour). The washers were detached and residual surface treatment was removed by gently wiping at least 3 times with separate cotton balls. The untreated sites on each arm were similarly wiped with a clean cotton ball.

Assessments: The ChromaMeter was used in this study to measure the reflective colors from the skin surface. Prior to the study, precision of the ChromaMeter operators was evaluated from replicate evaluations (5 readings, at least 3 minutes apart) of at least 4 untreated skin sites on each arm of at least 4 different subjects. The between-site CV% for each operator ranged between 4.51% and 11.13% (Section 5, Vol. 1.2).

The ChromaMeter operators measured the degree of blanching response at each site prior to treatment application (in duplicate) and at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after removal. All sites were assessed under standard fluorescent lighting and at room temperature. All assessments were made within 5 minutes of their scheduled time. The ChromaMeter operators were blinded to the duration of application at each site.

Food and Fluid

A meal was provided on the check-in day. Meals were served at traditional times thereafter; caffeine and alcohol were restricted during the study. Water was permitted *ad lib* throughout the study.

Subject Completion

A total of 15 subjects were entered into the study and all 15 subjects completed the study.

Data Analysis

ChromaMeter data: Negative areas under the response curve (AUECs) were determined from the a-scale readings of the ChromaMeter. The post-dose ChromaMeter reading at each site was first adjusted by subtracting the average value of the duplicate pre-dose (baseline) readings at that site to normalize for skin tone at different sites of each subject's forearms. To compensate for skin tone changes that occur over time, the average baseline-adjusted value for the untreated sites on each arm was subtracted from the baseline adjusted ChromaMeter value for each site on the same arm at each assessment time. These "corrected" baseline-adjusted ChromaMeter values were used in all subsequent analyses.

Results

Based on a population fitting technique used by the firm and the nonlinear mixed effect modeling used by the reviewer, the computed values of pharmacodynamic parameters are as follows:

Method	Parameter	Firm (A)	Reviewer (B) A/B	
ChromaMeter	ED ₅₀ (min)	61.7	61.1	1.01
	E _{max} (a scale units*min)	15.3	12.4	1.23

ED₅₀ based on the reviewer calculations is approximately 61 minutes. The firm employed an ED₅₀ duration of 60 minutes in the pivotal bioequivalence evaluation. A shorter duration of 30 minutes (D1) and a longer duration of 120 minutes (D2) were also included to determine "evaluable" subjects.

Determination of dose durations to be used in the pivotal study based on an ED₅₀ of 60 minutes is acceptable.

B. Pivotal study

The purpose of this study was to compare the relative vasoconstrictive effects of the test, fluticasone propionate cream, 0.05%, with the designated RLD, Cutivate^R (fluticasone propionate cream) 0.05% cream, in asymptomatic subjects.

Study No: 10236205

Applicant: Atrix Laboratories, Inc.

Study site: _____

Principal Investigator: _____, M.D., _____

Study dates:

- Group 1 (Subjects #1-21): 11/2/02
- Group 2 (Subjects #22-43): 11/9/02
- Group 3 (Subjects #44-72): 11/16/02
- Group 4 (Subjects #73-91): 11/30/02
- Group 5 (Subjects #92-141): 12/7/02

Study design One-period randomized design.

Subjects The hundred forty one (120 Caucasian, 8 Black, 7 Hispanic, 5 Asian, 1 Biracial) subjects who were chosen for participation in this study were healthy, non-tobacco-users (for 30 days prior to dosing), females in the age range of 18

to 47 years. They were within 20% of their ideal weight as specified in the protocol.

Screening of Subjects

Same as the pilot study

Drug

The following formulations were used in this study:

A. Test product

Fluticasone Propionate Cream, 0.05%, lot #1567A; lot size _____ manufactured by Atrix Laboratories, Inc., manufacture date 09/02.

B. Reference product Cutivate® Cream (fluticasone propionate), 0.05% , lot #2C278, manufactured by GlaxoSmithKline, Exp. 02/05.

Dosing

Randomization: The creams were applied to 6 sites on the flexor surface of each forearm determined by the randomization schedule. Two untreated (control) sites were also randomized on each forearm.

Staggered Application and Synchronized Removal

Eight (8) circular (approximately 1.6 cm diameter) application sites were designated on the flexor surface of each forearm between the wrist and the elbow. The sites were marked with number 1-8 on the right arm and 9-16 on the left arm from wrist to elbow for ease of identification. After baseline ChromaMeter (in duplicate) readings, an open washer was positioned over each site and taped to the forearm using hypo-allergenic paper tape on the sides of the washer.

Method of drug application was the same as mentioned in the pilot study.

Baseline assessments were started approximately 2 hours prior to the first application. The test and reference creams were applied to 6 sites on each arm; these treatments were applied 30 minutes (reference product only - D1), 60 minutes (test and reference products in duplicate) and 120 minutes (reference product only - D2) prior to removal. All sites were on, or staggered about, the midline axis of the subject's forearm and at least 3 cm from the wrist or antecubital fossa.

All applications were removed at the same time point (0-hour) with the shortest duration removed first. The washers

were detached and residual surface treatment was removed by gently wiping several times with cotton balls. The untreated sites were similarly wiped with clean cotton balls.

Assessment of Blanching

ChromaMeter operators and visual evaluators assessed the degree of blanching response at each site prior to treatment application and at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after removal. All assessments were made under standard fluorescent lighting and at room temperature. The 0-hour assessments were made within 15 minutes of their scheduled time and the 2 through 24-hour assessments were made within 5 minutes of their scheduled time. The ChromaMeter operators were blinded to the treatment and duration of application at each site. ChromaMeter assessments were based on the a-scale reading.

Data Evaluation and Results

Negative areas under the response curve for the ChromaMeter assessments were determined from the a-scale reading using a _____ ChromaMeter. ChromaMeter values were corrected for baseline and untreated site values.

The ratio of the mean area under the response curve for the reference 120 minutes duration (D2) to that of the 30 minutes duration (D1) was calculated for each subject. Subjects whose D2/D1 ratio was at least 1.25 were considered to be "evaluable" subjects and qualified for inclusion in the statistical analysis. The data from 47 subjects qualified for inclusion within this criterion using ChromaMeter results. Locke's Method for calculating confidence intervals was applied to the ChromaMeter and visual scoring results.

Results

A total of 141 subjects were entered into the study and all 141 subjects completed the study. There were 47 "evaluable subjects" based on the ChromaMeter results.

Evaluation of Bioequivalence

Mean ChromaMeter results for the fluticasone propionate cream, 0.05% (Atrix Laboratories, Inc.) vs. Cutivate® Cream (fluticasone propionate), 0.05%

(GlaxoSmithKline) using Locke's Method for calculating confidence intervals are shown below:

AUEC ₀₋₂₄		Test/Ref	90% CI
Test	Ref		
11.6	12.0	0.968	82.2-115.5

The 90% CI for AUEC₀₋₂₄ comparing the test and the reference products was within the acceptable range of 80-125%. The reviewer's calculations are similar to those submitted by the firm.

COMPONENTS AND COMPOSITION (Not To Be Released Under FOI)

The proposed commercial batch size is 8 times the ANDA batch size.

Components	Function	Formulation (%) w/w	ANDA Batch	Commercial Batch
Fluticasone propionate	Active	0.05	_____*	_____*
Propylene glycol, USP	/			
Sodium phosphate dibasic, USP				
Citric acid, USP				
Imidurea, NF				
Mineral oil, USP				
Isopropyl myristate, NF				
Cetostearyl alcohol, NF				
Ceteth-20				
Purified water, USP				

*Actual amount is based on drug potency (Found in the batch record).

Comments

1. The sponsor performed a pilot dose response study on the designated RLD (Cutivate® Cream 0.05%) based on the OGD guidance. Based on a population fitting technique of the chromaMeter dose-response data, an ED₅₀ of approximately 60 minutes was calculated. For the pivotal bioequivalence study, the sponsor used D₁, ED₅₀ and D₂ values of 30, 60 and 120 minutes, respectively. Based on the reviewer's analyses the selection of these values is appropriate.

2. One hundred forty one (141) subjects were dosed for the pivotal bioequivalence study and all subjects completed the study. There were 47 "evaluable subjects" for bioequivalence evaluation of the ChromaMeter dose-response data.

3. Based on the chromaMeter evaluation of skin blanching, the test product's AUEC₀₋₂₄ was 3.3% lower than that of the reference product. The 90% confidence intervals comparing the test and reference products were within the acceptable limit of 80-125%.

Deficiency Comment

The CEDR Guidance "Topical Dermatologic Corticosteroids: In Vivo Bioequivalence" (issued 6/2/1995, posted 3/6/1998), recommends that occlusion may be appropriate only for the lower potency products, e.g., potency groups VI and VII. Based on PDR 2003, studies performed with Cutivate® Cream indicate that it is in the medium range of potency as compared with other topical corticosteroids. In addition, the labeling for Cutivate® Cream, 0.05%, states that "the treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician".

The firm used occlusion in both the pilot and the pivotal studies, without submitting the evidence that reference product did not provide measurable vasoconstrictor response without occlusion. Therefore, the submitted studies are unacceptable. The firm may submit data to support occlusion used in the submitted studies. The data should be based on comparison of occluded and unoccluded skin sites treated the RLD.

Recommendation

The *in vivo* pharmacodynamic study conducted by Atrix Laboratories, Inc., on its fluticasone propionate cream, 0.05%, Lot #1567A, comparing it to the reference product, Cutivate® (fluticasone propionate) Cream 0.05%, Lot #2C278, has been found incomplete by the Division of Bioequivalence for the reason given in deficiency comment.

The firm should be informed of the above the deficiency comment and recommendation.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

Date: 11/19/03

RD INITIALED
FT INITIALED GJP SINGH

GJP Singh

Date 11-18-03

Concur:

Dale P. Conner

Dale P. Conner, Pharm.D.
Director

Division of Bioequivalence

Date: 11/19/03

Mmakary/ 11-17-03, 76633N1202.doc

cc: ANDA #76-633, original, HFD-658 (Makary), Drug File, Division File.

**APPEARS THIS WAY
ON ORIGINAL**

CC: ANDA #76-633
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh

Printed in final on 11/17/03
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Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary *MM*
HFD-658/ Bio team Leader G. Singh *CDPS - 11-18-03*
HFD-650/ D. Conner *DM 11/19/03*

BIOEQUIVALENCY - DEFICIENCIES submission date: December 31, 2002

- | | | |
|----|---|---------------------------------------|
| 1. | Pilot study
Clinical: _____ | Strengths: 0.05%
Outcome:IC |
| 2. | Pivotal pharmacodynamic study
Clinical: _____ | Strengths: 0.05%
Outcome:IC |

Outcome Decisions:IC

**APPEARS THIS WAY
ON ORIGINAL**

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-633

APPLICANT: Atrix Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Cream, 0.05%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

The CEDR Guidance "Topical Dermatologic Corticosteroids: In Vivo Bioequivalence" (issued 6/2/1995, posted 3/6/1998), recommends that occlusion may be appropriate only for the lower potency products, e.g., potency groups VI and VII. Based on PDR 2003, studies performed with Cutivate[®] Cream indicate that it is in the medium range of potency as compared with other topical corticosteroids. In addition, the labeling for Cutivate[®] Cream, 0.05%, states that "the treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician".

You used occlusion in both the pilot and the pivotal studies, without submitting the evidence that the reference product did not provide measurable vasoconstrictor response without occlusion. Therefore, the submitted studies are unacceptable. You may submit data to support that the occlusion used in your submitted studies was necessary. The data should be based on comparison of occluded and unoccluded skin sites treated with the RLD.

Sincerely yours,



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

ANDA: 76633
 EM Algorithm: NO COVARIABLES (08-11-2003 - 10:06:09)

Model : Emax model
 Measurement error variance : Homoscedastic
 EM termination criteria (Relative parameter change) : .1
 Marquardt precision on parameters : .001
 Relative parameter change for gradient calculation : .001

Initial population parameter estimates :

	Mean	Std. Dev.	C.V.%	Distrib.
C50	4.00733E+0 (5.499982E+1)	1.155759E+0	2.884114E+1 (1.674205E+2)	Log.Normal
EMAX	2.73429E+0 (1.53988E+1)	7.442647E-1	2.721967E+1 (8.602779E+1)	Log.Normal

Sigma = 82.21883

Nb of EM iterations : 4

Final population parameter estimates :

	Mean	Std. Dev.	C.V.%	Distrib.
C50	4.112141E+0 (6.107735E+1)	1.471642E+0	3.578773E+1 (2.778663E+2)	Log.Normal
EMAX	2.516121E+0 (1.238048E+1)	8.220298E-1	3.267052E+1 (9.82585E+1)	Log.Normal

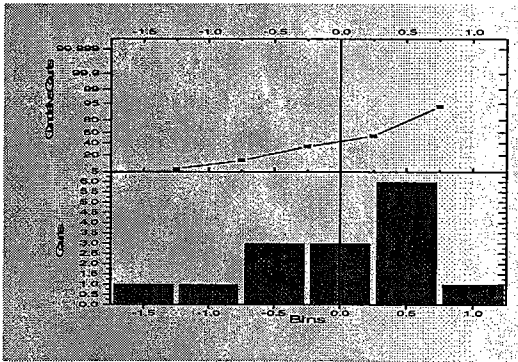
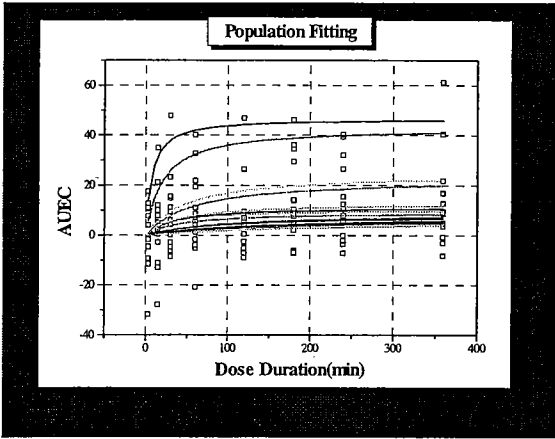
Sigma = 83.36902

Maximum Likelihood = -452.0931

AIC = 3.800776

Individual parameters

Subject	C50	EMAX	SUBJ
SUB1	181.0823	8.66371	1.
SUB2	20.17836	43.2702	2.
SUB3	43.47683	9.39248	3.
SUB4	7.01933	46.8544	4.
SUB5	40.78823	13.16888	5.
SUB6	218.9537	6.22358	6.
SUB7	179.5904	7.09968	7.
SUB8	35.35033	11.61809	8.
SUB9	56.42467	22.88241	9.
SUB10	92.91454	8.33488	10.
SUB11	96.72858	9.1492	11.
SUB12	26.80278	10.32566	12.
SUB13	49.21781	25.13035	13.
SUB14	124.7636	6.85156	14.
SUB15	116.3659	7.11192	15.
N	15.	15.	15.
Mean	85.97716	15.73847	8.
Min	7.01933	6.22358	1.
Max	218.9537	46.8544	15.
S.D.	65.89179	13.16226	
4.47214			
Var.	4341.72777	173.24509	20.
C.V.	76.63871	83.63115	
55.9017			



Residual Frequency Distribution Plot

ED50 Frequency Distribution Plot

APPEARS THIS WAY
ON ORIGINAL

GJP Singh	ANDA 76-633	
DBE/OGD	Chrom,	
	DETECT	
Date	8/11/2003	
Reviewer:	M. Makary	T/R
AVETest	11.57	0.97
AVEREF	11.96	
DTR	67.19	
DRR	118.95	
DTT	80.38	
Inta Sub Var		
(%)	-48	
K	0.50	
SQRT(K)	0.71	
W	0.02	
n	47	
t	1.6766	
t^2	2.81	
Gr	0.05	
DRR*W	2.53	
SQRT(DRR*W)	1.59	
+CINT	1.1548	
-CINT	0.8225	
90% CI:	115.48	82.25

Fluticasone propionate Cream
0.05%
ANDA #76-633
Reviewer: Moheb H. Makary
W. 76633STA1203.doc

Atrix Laboratories, Inc.
Fort Collins, Co.
Submission date:
December 5, 2003

Review of an Amendment

Executive Summary

The firm had previously submitted a pilot dose-response study and a pivotal bioequivalence study. The studies were found incomplete due to lack of justification for the use of occluded conditions.

The firm has now submitted data to support the occlusion used in its pilot and pivotal bioequivalence studies in its response to the comment made by the Division of Bioequivalence (DBE) in its letter of December 3, 2003. The data indicated that under occlusion conditions a greater and stable blanching response was generated compared to unoccluded conditions. The application is acceptable with no deficiencies.

Deficiency Comment stated in the December 3, 2003 letter and the firm's response:

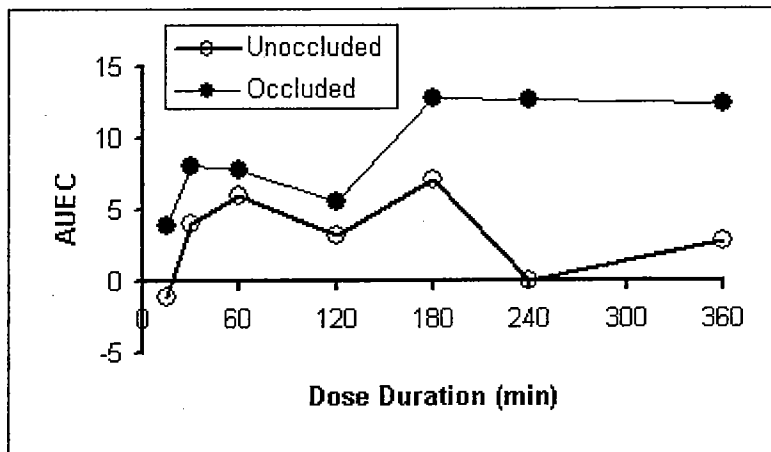
You used occlusion in both the pilot and the pivotal studies, without submitting the evidence that the reference product did not provide measurable vasoconstrictor response without occlusion. Therefore, the submitted studies are unacceptable. You may submit data to support that the occlusion used in your submitted studies was necessary. The data should be based on comparison of occluded and unoccluded skin sites treated with the RLD.

Firm's Response

The firm submitted data from a pilot dose response study based on comparison of occluded and unoccluded skin sites treated with the RLD. The results are shown in Table I.

Table I: Vasoconstrictor response (AUEC) under unoccluded and occluded conditions

Dose Duration (Min)	AUEC		B/A
	Unoccluded (A)	Occluded (B)	
15	-1.1	3.9	-3.55
30	4	8.1	2.03
60	6	7.8	1.30
120	3.2	5.6	1.75
180	7.1	12.8	1.80
240	0	12.7	> 12.7
360	2.8	12.3	4.39



The data demonstrate that when Cutivate® Cream 0.05% is unoccluded the blanching response is minimal and erratic at all time points, making it impossible to establish a meaningful dose-response relationship. Therefore, the conduct of the studies under occluded conditions was justified. Consequently, the firm's CRO, _____ conducted the studies under occluded conditions.

The firm's reply to the comment is acceptable.

Recommendation

1. The pilot dose response study conducted by Atrix Laboratories, Inc., on the designated RLD (Cutivate® Cream 0.05%) is acceptable.

2. The *in vivo* pharmacodynamic study conducted by Atrix Laboratories, Inc., on its fluticasone propionate cream, 0.05%, Lot #1567A, comparing it to the reference product, Cutivate® (fluticasone propionate) Cream 0.05%, Lot #2C278, has been found acceptable by the Division of Bioequivalence. The results of the vasoconstrictor study demonstrate that Atrix's fluticasone propionate cream, 0.05%, is bioequivalent to Cutivate® (fluticasone propionate) Cream 0.05%, manufactured by GlaxoSmithKline.

The firm should be informed of the above recommendation.

Moheb H. Makary
Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

Date: 1/22/04

RD INITIALLED
FT INITIALLED GJP SINGH

Gurpreet Singh
Date 1-22-04

Concur: *Barbara M. Sawit*
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 1/22/04

Mmakary/ 1-12-04, 1-15-04, 1-22-04, 76633N1203doc
cc: ANDA #76-633, original, HFD-658 (Makary), Drug File, Division File

**APPEARS THIS WAY
ON ORIGINAL**

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA #:76-633

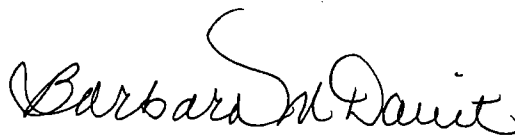
APPLICANT: Atrix Laboratories, Inc.

DRUG PRODUCTS: Fluticasone Propionate Cream, 0.05%

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

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

Sincerely yours,



Dale P. Conner, Pharm.D.

Director

Division of Bioequivalence

Office of Generic Drugs

Center for Drug Evaluation and Research

CC: ANDA #76-633
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-650/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh

V:\FIRMSAM\ATRIX\ltrs&rev\76633STA1203.doc
Printed in final on 1/22/04

Endorsements: (Final with Dates)

HFD-658/ Reviewer M. Makary *mm*

HFD-658/ Bio team Leader G. Singh *GPS 1-22-04*

HFD-650/ D. Conner *BW 1/22/04*

hr

BIOEQUIVALENCE - ACCEPTABLE submission date: December 5, 2003

1. Study Amendment (STA)

Clinical: _____

Strengths: 0.05%

Outcome: AC

Outcome Decisions: AC

**APPEARS THIS WAY
ON ORIGINAL**

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA #: 76-633	SPONSOR: Atrix Laboratories, Inc.
DRUG AND DOSAGE FORM:	Fluticasone Propionate Cream
STRENGTHS:	0.05%
TYPE OF STUDIES:	A Pilot Dose Response Study and a Pharmacodynamic Bioequivalence Study
CLINICAL STUDIES SITE:	<input type="checkbox"/> <input type="checkbox"/>
ANALYTICAL SITE:	N/A

STUDIES SUMMARY:	The studies are acceptable
DISSOLUTION TESTING:	N/A
WAIVERS:	N/A

DSI INSPECTION STATUS

Inspection needed: <u>No.</u>	Inspection status:	Inspection results:
First Generic: No.	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER: Moheb H. Makary, Ph.D.
SIGNATURE: *MM*

BRANCH: 3
DATE: 1/22/04

TEAM LEADER: G. Singh, Ph.D.
SIGNATURE: *Gurjapal*

BRANCH: 3
DATE: 1-22-04

for

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
SIGNATURE: *Barbara M. Saut* DATE: 1/22/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-633

ADMINISTRATIVE DOCUMENTS

Shimer, Martin

From: Davis, Gregory S
Sent: Wednesday, February 26, 2003 9:55 AM
To: CDER-OGDREG
Subject: FW: Pediatric Exclusivity has been granted

FYI

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

From: Parise, Cecelia M
Sent: Wednesday, February 26, 2003 9:55 AM
To: Ames, Timothy W; Davis, Gregory S; Grace, John F; Golson, Lillie D
Subject: FW: Pediatric Exclusivity has been granted

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

From: Carmouze, Grace N
Sent: Tuesday, February 25, 2003 5:44 PM
To: West, Robert L; Beitz, Julie G; Buehler, Gary J; Chen, Min Chu; Hixon, Dena R; Holovac, Mary Ann; Parise, Cecelia M; Patel, Paras M; Phucas, Kristin; Rickman, William P
Subject: Pediatric Exclusivity has been granted

Pediatric Exclusivity has been granted for the following drug product:

- Fluticasone

If there are any questions, please don't hesitate to contact me.

Grace Carmouze
Regulatory Health Project Manager
Division of Pediatric Drug Development, HFD-960
Office of Counter-Terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research
Food & Drug Administration

Phone: 301-827-7777
Fax: 301-827-7738

*Firm was informed (Kathy Gossard voice mail)
has been granted & that firm should provide an
amendment which recognizes this additional 6
months of exclusivity ~~and~~ that will attach to
patent # 4335121 & extend it's expiration until
5/14/03
Martin Shimer
26-Feb-2003*

APPLICATION REASSIGNMENT AUTHORIZATION FORM
OFFICE OF GENERIC DRUGS

ANDA/AADA#	DRUG	FIRM
76-633	Fluticasone Propionate Cream	Atrix

1. REASSIGN FROM: Team 3

DATE OF ORIGINAL ASSIGNMENT: _____

2. ASSIGN TO: Team 5

DATE OF REASSIGNMENT: _____

REASON FOR REASSIGNMENT: Distribution of workload
in Division I (ANDA is 129 days old)

[Signature]
BRANCH SUPERVISOR (SIGNATURE)

Shug Hon 5/15/03
DATE

[Signature]
CHEMISTRY/BIOEQUIVALENCE
DIVISION DIRECTOR (SIGNATURE)

CONCUR: NOT CONCUR:
DATE: 5/15/03

***A COPY OF THIS FORM SHOULD BE PLACED IN EACH APPLICATION
AND IN THE DIVISION FILE***

[Handwritten initials]
5.21.03

76-633 2.1

RECORD OF TELEPHONE CONVERSATION

<p>Reference is made to chemistry deficiency letter dated June 24, 2003. The firm wanted clarification on the following deficiencies:</p>	<p>DATE: July 28, 2003</p>
<p>3. Please add limits regarding _____ _____</p>	<p>ANDA NUMBER 76-633</p>
<p>Atrix: Are you asking for the _____ ? Also, should we ask the manufacturer to provide the test?</p>	<p>TELECON INITIATED BY SPONSOR</p>
<p>FDA: Yes (to both questions).</p>	<p>PRODUCT NAME: Fluticasone Propionate Cream, 0.05%</p>
<p>6. Regarding container/closure system, we have the following comments:</p>	<p>FIRM NAME: ATRIX LABORATORIES, INC.</p>
<p>b. Please provide test results for _____ of the tube. Test method should be provided.</p>	<p>FIRM REPRESENTATIVES: Lynn Hansen Cheri Jones _____ _____ _____</p>
<p>Atrix: Can we use information provided by the manufacturer of the tubes?</p>	<p>TELEPHONE NUMBER: 970-482-5868</p>
<p>FDA: Yes that is acceptable, however, we would prefer that you do the test yourself; at least for the first batch. It is good practice to have an S.O.P. for vendor validation. The _____ test would be sufficient.</p>	<p>FDA REPRESENTATIVES Shing Liu, Ph.D. Benjamin Lim, Ph.D. Wanda Pamphile, Pharm.D.</p>
<p>7. Regarding the bulk in-process control specifications, we have the following comments:</p>	<p>SIGNATURES: Shing Liu <i>SLL 8/6/03</i> Benjamin Lim <i>Ben Lim 8/6/03</i> Wanda Pamphile <i>WPF 8/6/03</i></p>
<p>a. Please add limits for _____ based on a validated method.</p>	
<p>b. Please add a procedure for _____ before packaging.</p>	
<p>Atrix: Please explain why you want us to add limits for the _____ test.</p>	
<p>FDA: The USP method is acceptable</p>	
<p>Atrix: It's assumed that _____</p>	
<p>FDA: We did not see the test results. The COA for the bulk was dated sometime in December, however the methods were done in September. Please explain.</p>	

Orig: ANDA 76-633
Cc: Division File
Chem. I Telecon Binder
V:\FIRMSAM\ATRIX\Telecon\76633.doc

RECORD OF TELEPHONE CONVERSATION

<p>8. Regarding the finished drug product specifications, we have the following comments:</p> <p style="margin-left: 40px;">a. Please add limits for _____ based on a validated method.</p> <p style="margin-left: 40px;">b. Please add limits for _____ based on validated methods.</p> <p>Atrix: The validated method is a USP method, and we will mention that in our response.</p> <p>FDA: That will be fine.</p> <p>11. The "alternate accelerated" condition is not acceptable as an accelerated stability study condition. The expiration dating will be based on the full term room temperature stability study data. Please provide the full term room temperature stability study data.</p> <p>Atrix: We spoke to Martin Shimer sometime ago and we were told that we can use alternate accelerated conditions.</p> <p>FDA: We will not accept _____ it is not in the FDA guidelines.</p> <p>Atrix: However, we _____</p> <p>FDA: You can get 18 months expiration, based on your current room temperature data. You can extend your expiration-dating period after approval by submitting a supplement.</p>	<p style="text-align: center;">DATE:</p> <p style="text-align: center;">July 28, 2003</p> <hr/> <p style="text-align: center;">ANDA NUMBER</p> <p style="text-align: center;">76-633</p> <hr/> <p style="text-align: center;">TELECON INITIATED BY SPONSOR</p> <hr/> <p style="text-align: center;">PRODUCT NAME:</p> <p style="text-align: center;">Fluticasone Propionate Cream, 0.05%</p> <hr/> <p style="text-align: center;">FIRM NAME:</p> <p style="text-align: center;">ATRIX LABORATORIES, INC.</p> <hr/> <p style="text-align: center;">FIRM REPRESENTATIVES:</p> <p style="text-align: center;">Lynn Hansen Cheri Jones _____ _____ _____</p> <hr/> <p style="text-align: center;">TELEPHONE NUMBER:</p> <p style="text-align: center;">970-482-5868</p> <hr/> <p style="text-align: center;">FDA REPRESENTATIVES</p> <p style="text-align: center;">Shing Liu, Ph.D. Benjamin Lim, Ph.D. Wanda Pamphile, Pharm.D.</p> <hr/> <p style="text-align: center;">SIGNATURES:</p> <p style="text-align: center;">Shing Liu Benjamin Lim Wanda Pamphile</p>
--	--

Orig: ANDA 76-633

Cc: Division File

Chem. I Telecon Binder

V:\FIRMSAM\ATRIX\Telecon\76633.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-633
Drug Fluticasone Propionate Cream

Applicant Atrix Laboratories, Inc.
Strength(s) 0.05%

APPROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch

Date 19 April 2004
Initials MS

Date 4/26/04
Initials MS/for

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

Patent/Exclusivity Certification: Yes No
If Para. IV Certification- did applicant

RLD = NDA# 19-958
Date Checked 4/26/04

Notify patent holder/NDA holder Yes No

Nothing Submitted

Was applicant sued w/in 45 days: Yes No

Written request issued

Has case been settled: Yes No

Study Submitted

Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes No

Date settled: Pediatric exclusivity previously granted

Type of Letter:

Comments:

Eligible for TA

Deal cut to '12 patent expires 5/14/2004

2. Project Manager, Wanda Pamphile Team 5
Review Support Branch

Date 4-16-04
Initials WP

Date 4-21-04
Initials WP

Original Rec'd date 12-31-02
Date Acceptable for Filing 1-2-03 ✓
Patent Certification (type) III
Date Patent/Exclus. expires 5-14-04

EER Status Pending Acceptable OAI
Date of EER Status 3-10-03
Date of Office Bio Review 1-22-04
Date of Labeling Approv. Sum 3-24-04
Date of Sterility Assur. App. N/A

Citizens' Petition/Legal Case Yes No
(If YES, attach email from PM to CP coord)

Methods Val. Samples Pending Yes No

First Generic Yes No

MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No

Modified-release dosage form: Yes No

Suitability Petition/Pediatric Waiver

Interim Dissol. Specs in AP Ltr: Yes

Pediatric Waiver Request Accepted Rejected Pending

Previously reviewed and tentatively approved Date _____

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

Comments:

3. Div. Dir./~~Deputy Dir.~~
Chemistry Div. I ~~or II~~
Comments:

Date 4/23/04
Initials IRAC

The CMC section is satisfactory for TA

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

Date _____
Initials _____

N/A. ANDA 76-300 (Altara) was tentatively approved on 2/27/03 for Fluticasone Ointment.

REVIEWER:

FINAL ACTION

5. Gregg Davis
Deputy Dir., DLPS

Date _____
Initials _____

KLD = Citivate Cream 0.05%
PaxoSmithKline

NDA 19-958 (001)

6. Peter Rickman
Director, DLPS

Date 4/26/04
Initials PR

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

Comments: Acceptable EES dated 3/10/03 (Verifical 4/26/04) NDA I. Labels noted. Bioequivalence studies (pilot dose response study and the pivotal BEST study) found acceptable 1/22/04. Study performed by _____

This facility has an acceptable DSI inspectional history. Offres. done/bioassayed 1/22/04. Labeling found acceptable in final print 3/24/06. QIC found acceptable 4/1/04. Methods validation will not be requested - does not meet current criteria

6. Robert L. West
Deputy Director, OGD

Date 4/26/04
Initials R West

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

Comments: Arix made a paragraph III certification to the '12 patent that was due to expire on 11/14/03. This patent was effectively extended until 5/14/03 upon the granting of pediatric exclusivity to GSK for Citivate (Fluticasone). Arix has addressed the pediatric extension.

This ANDA may be granted a tentative approval (pending the expiration of GSK's pediatric exclusivity on 5/14/04).

7. Gary Buehler
Director, OGD

Date 4/26/04
Initials GB

Comments: 7 for Ointment
First Generic Approval PD or Clinical for BE Special Scientific or Reg. Issue

8. Project Manager, Team Wanda Pamphile
Review Support Branch 5

Date 4/26/04
Initials W

Date PETS checked for first generic drug (just prior to notification to firm) _____
Applicant notification: _____

11:45 Time notified of approval by phone 11:54 Time approval letter faxed
FDA Notification: _____

4/26/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
4/26/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-633

Applicant Atrix Laboratories, Inc.

Drug Fluticasone Propioante Cream

Strength(s) 0.05%

PROVAL TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch

Date 7 May 04
Initials MS

Date 5/10/04
Initials [Signature]

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

Patent/Exclusivity Certification: Yes No
If Para. IV Certification- did applicant

RLD = 19-958
Date Checked Previously granted
Nothing Submitted

Notify patent holder/NDA holder Yes No

Written request issued

Was applicant sued w/in 45 days: Yes No

Study Submitted

Has case been settled: Yes No

Date settled:

Is applicant eligible for 180 day

Generic Drugs Exclusivity for each strength: Yes No

Type of Letter:

Comments:

eligible for (FA) upon exp of prod ext to '121 patent w/ 5/14/2001

2. Project Manager, Wanda Pamphile Team 5
Review Support Branch

Date 5-5-04
Initials WP

Date 5-10-04
Initials WP

Original Rec'd date 12-31-02
Date Acceptable for Filing 1-2-03 ✓
Patent Certification (type) II
Date Patent/Exclus. expires N/A

EER Status Pending Acceptable OAI
Date of EER Status 3-10-03
Date of Office Bio Review 1-22-04
Date of Labeling Approv. Sum 3-24-04
Date of Sterility Assur. App. N/A

Citizens' Petition/Legal Case Yes No

(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes No

First Generic Yes No

MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No

Modified-release dosage form: Yes No

Suitability Petition/Pediatric Waiver

Interim Dissol. Specs in AP Ltr: Yes

Pediatric Waiver Request Accepted Rejected Pending

Previously reviewed and tentatively approved

Date 4-26-04

Previously reviewed and CGMP def. /NA Minor issued

Date _____

Comments:

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

Date _____
Initials _____

N/A

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

Date 5/11/04
Initials DK/ed

No change in CMC since TA. Remains satisfactory for final approval.

REVIEWER:

FINAL ACTION

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

Date _____
Initials _____

NA. Multiple ANDAs have been tentatively approved for this drug product.

6. Vacant
Deputy Dir., DLPS

*RD- Cotivate Cream 0.05%
GlaxoSmithKline NDA 19-958 (001)*

Date _____
Initials _____

7. Peter Rickman
Director, DLPS

Date 5/12/04
Initials PR

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

Comments: *Acceptable EES data 3/11/03 (verified 5/12/04). No OAI alerts noted. Refers to the administrative sign-off form completed at the time of the tentative approval granted on 4/26/04. On 4/27/04, Ateix submitted a minor amendment providing a paragraph II certification to the '121 patent and requested final approval of the ANDA. OTC remains acceptable 5/10/04. Methods validation was not requested - does not meet current criteria.*

Robert L. West
Deputy Director, OGD

Date 5/13/2004
Initials RLW

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

Comments: *Ateix made a paragraph III certification to the '121 patent that expired on 11/14/03. However, prior to the expiration of the '121 patent, GSK was awarded pediatric exclusivity for the RD, Cotivate. This effectively extended the patent until 5/14/04. This ANDA is recommended for final approval upon the expiration of GSK's exclusivity, i.e., May 14, 2004.*

9. Gary Buehler
Director, OGD
Comments:

Date 5/14/04
Initials GB

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

10. Project Manager, Wanda Pamphile
Team 5

Date 5/14/04
Initials WP

Review Support Branch
Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
10:25 Time notified of approval by phone 10:30 Time approval letter faxed

FDA Notification:
5/14/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
5/14/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-633

CORRESPONDENCE

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



PHONE: (970) 482-5868
FAX: (970) 482-9735
<http://www.atrixlabs.com>

VIA FEDERAL EXPRESS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

December 31, 2002

RE: **Fluticasone Propionate Cream, 0.05%
Original Abbreviated New Drug Application**

505(j)(2)(A) OK
26-FEB-2003
Mugony D. Davis

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an Abbreviated New Drug Application for Fluticasone Propionate Cream, 0.05% as required by Section 505 (j) of the Federal Food, Drug and Cosmetic Act, and in accordance with 21 CFR Part 314.92 and 314.94.

Pursuant to 21 CFR 314.94(a)(2), each volume contains a comprehensive table of contents indicating the page number(s) of the submission's contents. The blue archival and red Chemistry copies (1 volume each) contain the complete application. The orange Bioavailability/Bioequivalence section review copy and archival copy (2 copies each) contain the Bioequivalence information.

The Methods Validation package is provided in a brown folder and contains duplicate copies of the raw material and finished product specifications, methods and analytical results. Atrix Laboratories, Inc. commits to resolve any issues identified in the methods validation process post-approval.

This information is submitted for your review and approval. Please acknowledge receipt of this submission by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

A handwritten signature in cursive script that reads "David W. Osborne".

David W. Osborne, Ph.D.
Atrix Laboratories, Inc.
Vice President, Dermatology Division

RECEIVED

JAN 02 2003

OGD / CDER

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



PHONE: (970) 482-5868
FAX: (970) 482-9735
<http://www.atrixlabs.com>

VIA FEDERAL EXPRESS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

AMENDMENT

NEW CORRESP

NC

February 24, 2003

**RE: ANDA # 76-633 Fluticasone Propionate Cream, 0.05%
Amendment- labeling**

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Fluticasone Propionate Cream, 0.05% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Reference is made to communications between Martin Schimer of FDA and Kathy Coressel of Atrix on February 14 and 19, 2003. Please see Atrix's NOTE TO FILE write up of the communications provided in ATTACHMENT 1.

As requested the following is provided:

ATTACHMENT 2: cGMP Certifications for the outside labs.

ATTACHMENT 3: Side-by-side labeling comparison for outsert.

This information is submitted for your review and approval. Please acknowledge receipt of this submission by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,
Atrix Laboratories, Inc.

Kathy Coressel
Regulatory Project Leader
Enclosures

RECEIVED

FEB 25 2003

OGD / CDER

ANDA 76-633

FEB 26

Atrix Laboratories, Inc.
Attention: David W. Osborne, Ph.D.
2579 Midpoint Drive
Fort Collins, CO 80525
|||||

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 conversations dated February 14, 2003 and February 19, 2003 and your correspondence dated February 24, 2003.

NAME OF DRUG: Fluticasone Propionate Cream, 0.05%

DATE OF APPLICATION: December 31, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 2, 2003

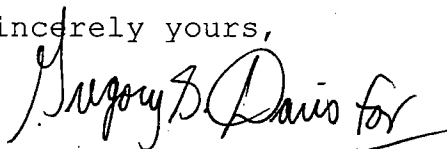
We will correspond with you further after we have had the opportunity to review the application.

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,



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

ANDA 76-633

cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB *G Davis* 26 FEB 2003 date
HFD-615/MShimer, CSO *M Shimer* 25 February 2003 date
Word File V:\Firmsam\Atrix\Ltrs&rev\76633.ack
F/T EEH 02/25/03
ANDA Acknowledgment Letter!

**APPEARS THIS WAY
ON ORIGINAL**

1000



2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.

ATRIX
LABORATORIES, INC.

PHONE: (970) 482-5868
FAX: (970) 482-9735
http://www.atrixlabs.com

VIA EXPRESS MAIL

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

NOTE
MMS
4-28-03

**UNSOLICITED
AMENDMENT
NEW CORRESP**

No

April 17, 2003

**RE: ANDA 76-633 Fluticasone Propionate Cream, 0.05%
Unsolicited Amendment- Change in signature responsibility.**

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Fluticasone Propionate Cream, 0.05% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Atrix Laboratories, Inc has hired a Vice President of Regulatory Affairs, Cheri Jones. Ms. Jones will now be assuming the responsibility of signing all correspondences. Please direct all correspondence to the attention of Cheri Jones.

Cheri Jones can be reached by phone at (970) 212-4901.
The fax number is (970) 482-9734.
Email: cjones@atrixlabs.com

Thank you in advance for your cooperation and we are sorry for any inconvenience.

Sincerely,

Cheri Jones, M.S., RAC
Atrix Laboratories
V.P. Regulatory Affairs

RECEIVED

APR 21 2003

OGD / CDER

MINOR AMENDMENT

ANDA 76-633

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

JUN 24 2003



APPLICANT: Atrix Laboratories, Inc.

TEL: 970-212-⁴⁹⁰¹~~4834~~

ATTN: ~~Kathy Corcosel~~
Cheri Jones

FAX: 970-482-973~~X~~
A

FROM: Wanda Pamphile

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 31, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Cream, 0.05%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

Chemistry comments included. Please include in response.

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

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

WF 6/24/03

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of trade secret and/or

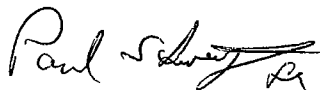
confidential commercial

information from

6/24/2003 FDA FAX

- b. Please provide the pH specification.
 - c. The test and specifications presented on the regulatory stability protocol (p. 506) and regulatory shelf-life specifications (p. 507) are different. Please clarify.
11. The "alternate accelerated" condition is not acceptable as an accelerated stability study condition. The expiration dating will be based on the full term room temperature stability study data. Please provide the full term room temperature stability study data.
 12. Please provide additional stability study to justify the labeling storage conditions (2° - 30°C).
- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. The bioequivalence portion of your submission is under review. Deficiencies, if any, will be communicated to you under separate cover.
 2. The labeling portion of your submission is under review. Deficiencies, if any, will be communicated to you under separate cover.
 3. We will issue a method validation request to an FDA laboratory, when all testing issues are resolved. Please commit to work with the Agency to expeditiously resolve any deficiencies from the method validation study if the ANDA is approved prior to its completion.
 4. The firms referenced in your application must be in compliance with cGMP at the time of approval.
 5. Please provide any available drug product room temperature stability data.

Sincerely yours,



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

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



PHONE: (970) 482-5868
FAX: (970) 482-9735
<http://www.atrixlabs.com>

Ms. Wanda Pamphile
Office of Generic Drugs
7500 Standish Place, Room 150
Rockville, MD 20855-2773
FAX: (301) 594-0180

July 09, 2003

Re: Request for Teleconference - ANDA 76-633: Questions for FDA on Fluticasone Propionate Cream, 0.05% CMC deficiency letter received on 6/24/03.

Ms. Pamphile:

As requested in a telephone conversation last week Atrix is requesting further clarification on the following listed concerns presented in the letter from the Agency on June 24, 2003. Atrix is in the process of finalizing the remaining concerns addressed in the letter and would appreciate a call as soon as possible to discuss the following.

The following are numbered as they appear in the June 24, 2003 letter.

5. Regarding container/closure system, we have the following comments:

b. Please provide tests results for _____
_____ of the tube. Test method should be provided.

Please provide further explanation of what FDA expects.

7. Regarding the bulk in-process control specifications, we have the following comments:

a. Please add limits for _____ based on a **validated** method.

_____ will be implemented based on the methodology stated in USP.
Please clarify the need to validate.

c. Please add a procedure for _____ before packaging.

The Bulk Production Record does have a step _____ that indicates

--	--

8. Regarding the finished product drug specifications, we have the following comments:

- a. Please add the limits for _____ based on a **validated** method.
- b. Please add limits for _____ based on **validated** methods.

These test are directly from USP please clarify the need to validate.

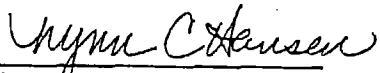
11. The "alternate accelerated" condition is not acceptable as an accelerated stability study condition. The expiration dating will be based on the full term room temperature stability study data. Please provide the full term room temperature stability data.

Communication between Atrix and FDA, Martin Schimer, February 14, 2003, discussed the change in the accelerated temperature for this specific product. FDA including chemistry reviewer were satisfied with the change to _____ conditions as the accelerated storage condition. Please confirm.

Please contact me at (970) 212-4894 or lhansen@atrixlabs.com with the time and date of the telephone conversation to further discuss the concerns listed above.

Thank you in advance for your assistance.

Regards,



Lynn C. Hansen
Atrix Laboratories, Inc.
Regulatory Affairs

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 482-9734
<http://www.atrilabs.com>

Ms. Wanda Pamphile
Office of Generic Drugs
7500 Standish Place, Room 150
Rockville, MD 20855-2773
FAX: (301) 594-0180

July 25, 2003

Re: **Teleconference** - ANDA 76-633: Questions for FDA on Fluticasone Propionate Cream, 0.05% CMC deficiency letter received on 6/24/03.

Ms. Pamphile:

Thank you for the scheduled telephone call for Monday, July 28, 2003. The telephone number to call is (970) 212-4422. The analytical chemists responsible for finished product and raw material, and our packaging representative will be joining me during both telephone calls.

I would also like to add another question, #3 presented in the June 24, 2003 deficiency letter for this ANDA.

3. Please add limits regarding _____

I look forward to talking with you on Monday. Please contact me at (970) 212-4894 or lhansen@atrilabs.com if there are any questions or concerns.

Again thank you in advance for your assistance.

Regards,

Lynn C. Hansen
Atrix Laboratories, Inc.
Regulatory Affairs

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 482-9734
<http://www.atrixlabs.com>

Ms. Wanda Pamphile
Office of Generic Drugs
7500 Standish Place, Room 150
Rockville, MD 20855-2773
FAX: (301) 594-0180

July 28, 2003

Re: **Teleconference - Discussion - ANDA 76-633: FDA Clarifications for Fluticasone Propionate Cream, 0.05% CMC deficiency letter received on 6/24/03.**

Participants: FDA: Benjamin Lim, Chemist, Shing Liu, Team Leader, Wanda Pamphile, Project Manager
Atrix: Cheri Jones, VP Regulatory Affairs, Lynn Hansen, Regulatory Affairs, _____, Analytical Product, _____ QA Analytical Raw Materials, _____, Package Engineering

Ms. Pamphile:

Atrix Laboratories Inc. would like to formally thank you for your assistance in setting up the teleconference held today. The discussion was scheduled to provide clarification to various questions detailed in the letter from the Agency on June 24, 2003.

The following numbered questions are presented as they appear in the June 24, 2003 letter.

3. Please add limits regarding _____

Atrix will add the requested limits, i.e. molecular weight, etc.

5. Regarding container/closure system, we have the following comments:

b. Please provide tests results for _____ of the tube. Test method should be provided.

Further information from _____ has been obtained by the Packaging Department since this question was submitted. The



ANDA 76-633
Telecon Minutes 7/28/03
Page 2

Atrix will prepare internal documents to accommodate the recording of the _____ test results from the supplier's Certificate of Conformance. Atrix will also conduct the test on the first validation lot with tubes utilizing the method from a supplier.

7. Regarding the bulk in-process control specifications, we have the following comments:

- a. Please add limits for _____ based on a **validated** method.

The specifications and USP methodology for _____ will be added to the bulk-in process controls for the cream. (There is no need for the validation of the USP methods.)

- c. Please add a procedure for _____ before packaging.

Although the Bulk Production Record does have a step _____ that

[_____]

[_____]

8. Regarding the finished product drug specifications, we have the following comments:

- a. Please add the limits for _____ based on a **validated** method.
b. Please add limits for _____ based on **validated** methods.

The specifications and USP methodology for _____ and _____ will be added to the finished product drug specifications for the cream. (There is no need for the validation of the USP method.)

11. The "alternate accelerated" condition is not acceptable as an accelerated stability study condition. The expiration dating will be based on the full term room temperature stability study data. Please provide the full term room temperature stability data.

Although there was discussion with FDA (Martin Schimer, February 14, 2003).

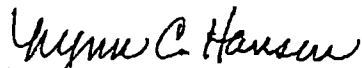
Full term room temperature stability data will be submitted for the determination of the expiration-dating period (i.e. 18 months at room temperature will be 18 months expiration).

ANDA 76-633
Telecon Minutes 7/28/03
Page 3

Please contact me at (970) 212-4894 or lhansen@atrixlabs.com if there are any additional comments.

Thank you again for your assistance in arranging the telephone call in a timely and efficient manor.

Regards,



Lynn C. Hansen
Atrix Laboratories, Inc.
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



PHONE: (970) 482-5868
FAX: (970) 482-9735
http://www.atrilabs.com

VIA FEDERAL EXPRESS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

MINOR
AMENDMENT

ORIGINAL AMENDMENT

N/A

October 06, 2003

**RE: ANDA 76-633 – Fluticasone Propionate Cream, 0.05%
Minor Amendment - CMC**

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Fluticasone Propionate Cream, 0.05% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Reference is made to FDA communication dated June 24, 2003. Please find a copy of this FDA communication provided in Attachment 1.

A response is provided for each deficiency in the order presented in the above referenced communication.

A. Deficiencies

1. The Drug master File No. _____ was found deficient. The DMF holder has been notified. Please do not respond to this letter until you have been informed by the DMF holder that all deficiencies have been addressed.

Atrix Response: Attachment 2 contains a copy of the first page from the response sent to FDA for Drug Master File _____.

2. Regarding the drug substance, we have the following comments:

Atrix Response: Provided in Attachment 3 are the updated drug substance specification, 01158, and updated Certificate of Analysis for Fluticasone Propionate. The following FDA comments, a-f, have been incorporated into the updated documents.

- a. Please add the _____ test and limits based on a validated method.

OCT 06 2003

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Handwritten signature/initials

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10/6/2003 ATRIX LETTER

- C Updated additional information on documents originally submitted in this ANDA.
1. The Drug Establishment Registration information provided on page 106 of the submission was incorrectly identified for the laboratory facility and administrative offices location at Midpoint Drive, Fort Collins, CO. Atrix Laboratories, Inc. only Drug Establishment Registration Number is 1722158.

This information is submitted for your review and approval. Please acknowledge receipt of this submission by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

If there are further concerns or comments please feel free to call me at (970) 212-4901 or at cjones@atrixlabs.com.

Sincerely,

A handwritten signature in black ink that reads "Cheri Jones". The signature is written in a cursive style with a long horizontal flourish extending to the right.

Cheri Jones, M.S., RAC
Atrix Laboratories, Inc.
Vice President Regulatory Affairs

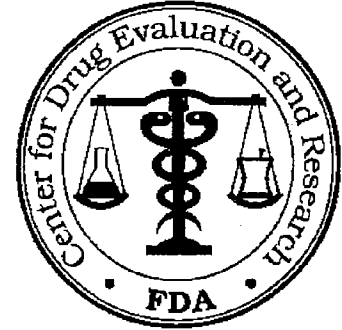
**APPEARS THIS WAY
ON ORIGINAL**

BIOEQUIVALENCY AMENDMENT

ANDA 76-633

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

DEC - 3 2003



APPLICANT: Atrix Laboratories, Inc.

TEL: 970-212-4901

ATTN: Cheri Jones

FAX: 970-482-9734

FROM: Beth Fritsch

PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 31, 2002, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Cream, 0.05%.

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

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. **Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket.** Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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BIOEQUIVALENCY DEFICIENCIES

DEC -8 1998

ANDA: 76-633

APPLICANT: Atrix Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Cream, 0.05%

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

The CEDR Guidance "Topical Dermatologic Corticosteroids: In Vivo Bioequivalence" (issued 6/2/1995, posted 3/6/1998), recommends that occlusion may be appropriate only for the lower potency products, e.g., potency groups VI and VII. Based on PDR 2003, studies performed with Cutivate[®] Cream indicate that it is in the medium range of potency as compared with other topical corticosteroids. In addition, the labeling for Cutivate[®] Cream, 0.05%, states that "the treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician".

You used occlusion in both the pilot and the pivotal studies, without submitting the evidence that the reference product did not provide measurable vasoconstrictor response without occlusion. Therefore, the submitted studies are unacceptable. You may submit data to support that the occlusion used in your submitted studies was necessary. The data should be based on comparison of occluded and unoccluded skin sites treated with the RLD.

Sincerely yours,



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

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



PHONE: (970) 482-5868
FAX: (970) 482-9735
http://www.atrilabs.com

VIA FEDERAL EXPRESS

Dale P. Conner, Pharm.D
Director, division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research
Metro Park North 2, Room 150
7500 Standish Place

BIOEQUIVALENCY AMENDMENT

December 5, 2003

ORIG AMENDMENT

N/AB

**RE: ANDA 76-633 – Fluticasone Propionate Cream, 0.05%
Dose Response Study data**

Dear Dr. Connor:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Fluticasone Propionate Cream, 0.05% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Reference is made to FDA communication dated December 3, 2003. Please find a copy of this FDA communication provided in Attachment 1.

We have contacted _____, the study center site and have been provided information supporting the need to conduct the submitted Bioequivalency study on this application under occlusion.

Data to support that occlusion used in our submitted study was necessary, please find enclosed:

1. **Table A:** UNOCCLUDED RESULTS FROM A DOSE RESPONSE VASOCONSTRICTOR STUDY WITH CUTIVATE (FLUTICASONE PROPIONATE CREAM) CREAM 0.05% (GLAXO WELLCOME INC.), CONDUCTED BY _____ and

ORIGINAL

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DEC 08 2003

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2. **Table B:** OCCLUDED RESULTS FROM A DOSE RESPONSE
VASOCONSTRICTOR STUDY WITH CUTIVATE (FLUTICASONE
PROPIONATE CREAM) CREAM 0.05% (GLAXO WELLCOME INC.)
CONDUCTED BY _____.

This data demonstrates that when Cutivate Cream 0.05% is unoccluded the blanching response is extremely minimal and erratic at all time points, making it impossible to calculate a meaningful Emax or ED50 time. Consequently, our CRO, _____, felt it necessary to conduct the trials under occluded conditions.

We requested and received a letter from Dr. _____ discussing this issue which is included as Attachment III. If you require the complete report from the unoccluded study, please contact Dr. _____, and he will forward you a copy as this is Confidential data as it was conducted for another company. If this is inconvenient for you, we could relay this request to Dr. _____, if required.

Please advise if there is further information needed to satisfy your request. Please feel free to contact me at 970-212-4901 or email: cjones@atrixlabs.com.

Sincerely,

ATRIX LABORATORIES, INC.


Cheri Jones, M.S., RAC
Vice-President Regulatory Affairs

MODE = MEMORY TRANSMISSION

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END=DEC-19 10:52

FILE NO.=938

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U.S. Department of Health and Human Services

Food and Drug Administration

{PRIVATE}

Fax Cover Sheet

Public Health Service
Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling & Program Support
Labeling Review Branch
Rockville, Maryland 20855

To: Cheri Jones

DATE: December 19, 2003

Fax: 970-482-9734

Phone: 970-212-4901

SUBJECT: ANDA 76-633

From: Melaine Shin, R.Ph., Labeling Reviewer

Phone: (301) 827-5846

Fax: (301) 594-1174

Number of Pages:
(Including Cover Sheet)

Comments: Please send me a desk copy of your submission responding to this letter.

Attention: Melaine Shin
Room E124

*This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, immediately notify us by telephone and return it to us at the above address by mail. Thank you.

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.

*Firm response
will respond
to deficiency
letter sent on
2/4/04
Reviewer should look
@ the Citricubans
and minor amend
time minor amend
2/4/04*



ATRIX
LABORATORIES, INC.

ANDA 76-633
Atrix Laboratories, Inc.

Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 482-9734
<http://www.atrixlabs.com>

VIA FEDERAL EXPRESS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

**UNSOLICITED MINOR
AMENDMENT**

February 03, 2004

ORIG AMENDMENT

N/A

**RE: ANDA 76-633 – Fluticasone Propionate Cream, 0.05%
Unsolicited Minor Amendment - CMC**

Dear Mr. Buehler:

Atrix Laboratories, Inc. (ATRIX) is hereby submitting an unsolicited minor amendment to our unapproved Abbreviated New Drug Application for Fluticasone Propionate Cream, 0.05%.

ATRIX has reviewed the submitted documentation and compiled deficiencies that have been presented by FDA chemistry reviewers on other ANDAs currently under review and are updating this ANDA for completeness based upon those comments. Documents submitted to this ANDA are updates to the documents sent on October 06, 2003 in answer to a deficiency letter.

1. The Raw Material Specification (01.158) for the active drug substance has been updated with the following changes:
 - Two updates have taken place:

i.

ii.



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2/3/2004 ATRIX LETTER

If there are further concerns or comments please feel free to call me at (970) 212-4901 or at: cjones@atrixlabs.com.

Sincerely,

ATRIX LABORATORIES, INC.

A handwritten signature in black ink that reads "Cheri Jones". The signature is written in a cursive style with a large initial "C" and a long, sweeping underline.

Cheri Jones, M.S., RAC
Vice President Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 482-9734
<http://www.atrixlabs.com>

VIA FEDERAL EXPRESS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and
Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

AMENDMENT TO PENDING ANDA

February 03, 2004

**RE: ANDA 76-633 – Fluticasone Propionate Cream, 0.05%
Amendment to Pending Application
Final Printed Labeling**

NIAF

Dear Mr. Buehler:

Atrix Laboratories, Inc. (ATRIX) is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Fluticasone Propionate Cream, 0.05%.

In response to the label review letter of December 19, 2003, Atrix has updated the labeling to include all comments contained in that communication and are providing three CD-ROMS with the labeling provided in electronic format for ease of review.

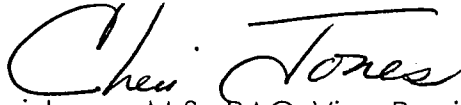
To facilitate review we are also providing, as requested, the side-by-side comparison of all changes and updates, annotated and explained.

The submission contains required signed original documents to accompany the electronic version of the final printed labeling, in accordance with FDA-OGD guidelines. This electronic submission is provided on one CD-ROM, approximately 12 MB. ATRIX certifies that the CD-ROM has been scanned for viruses using Symantec Antivirus Corporate Edition version 8.00.0.9347 with current virus definitions and is virus free.

If there are any further questions or comments, please feel free to contact me at 970-212-4901 or fax 970-482-9734.

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FEB 04 2004
OGD/CDER

Sincerely,

A handwritten signature in cursive script that reads "Cheri Jones". The signature is written in black ink and is positioned above the typed name.

Cheri Jones, M.S., RAC, Vice President Regulatory Affairs

Desk Copy to: Melaine Shin, R.Ph., Labeling Reviewer, Room E124

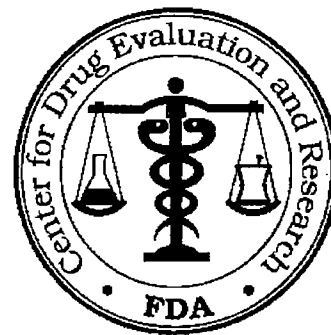
**APPEARS THIS WAY
ON ORIGINAL**

MINOR AMENDMENT

ANDA 76-633

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

FEB 04 2004



APPLICANT: Atrix Laboratories, Inc.

TEL: 970-212-4901

ATTN: Cheri Jones

FAX: 970-482-9734

FROM: Wanda Pamphile

PROJECT MANAGER: (301) 827-5763

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 31, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Cream, 0.05%.

Reference is also made to your amendment(s) dated: October 6 and December 5, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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

SPECIAL INSTRUCTIONS:

Chemistry comments included. Please include in response.

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

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

WP
2/4/04

FEB 04 2004

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-633

APPLICANT: Atrix Laboratories, Inc.

DRUG PRODUCT: Fluticasone Propionate Cream, 0.05%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (DMF) No. _____ remains inadequate. The DMF holder has been notified. Please do not respond to this letter until you have been informed by the DMF holder that all deficiencies have been addressed.

2.

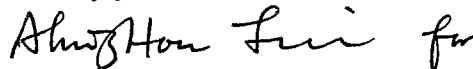
3.

4.

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

Please provide any available drug product room temperature stability data.

Sincerely yours,



Rashmikant M. Patel, Ph.D.

Director

Division of Chemistry I

Office of Generic Drugs

Center for Drug Evaluation and Research

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



4-1
Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 482-9734
http://www.atrilabs.com

February 19, 2004

VIA FEDERAL EXPRESS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

MINOR AMENDMENT

ORIG AMENDMENT

N/AM

**RE: ANDA 76-633 – Fluticasone Propionate Cream, 0.05%
Minor Amendment - CMC**

Dear Mr. Buehler:

Atrix Laboratories, Inc. (ATRIX) is hereby submitting a minor amendment to our unapproved Abbreviated New Drug Application for Fluticasone Propionate Cream, 0.05% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

ATRIX has provided updated information in an Unsolicited Minor Amendment filed to the Agency on February 03, 2004. Included in this amendment are updated documents addressing the remaining issues identified in the February 04, 2004 communication received from the Agency.

Reference is made to FDA communication dated February 04, 2004. Please find a copy of the FDA communication provided in **Attachment 1**.

A response is provided with each deficiency in the order presented in the above referenced communication.

A. Deficiencies

1. Drug Master File (DMF) No. _____ remains inadequate. The DMF holder has been notified. Please do not respond to this letter until you have been informed by the DMF holder that all deficiencies have been addressed.

Atrix Response: _____, the DMF holder, has provided a copy of the response sent to the agency on February 17, 2004. A copy of the letter is provided in **Attachment 2**.

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Atrix Response: The comments above have been addressed in the Unsolicited Minor Amendment submitted on February 03, 2004.

B. Acknowledgement

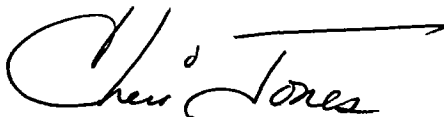
Updated long-term stability data (18 month) for exhibit batch 1567, packaged in the proposed marketing presentations, will be filed to this ANDA in March 2004, when 18 month stability test results are available.

This information is submitted for your review and approval.

If there are further concerns or comments please feel free to call me at (970) 212-4901 or at: cjones@atrixlabs.com.

Sincerely,

ATRIX LABORATORIES, INC.



Cheri Jones, M.S., RAC
Vice President Regulatory Affairs

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 482-9734
<http://www.atrixlabs.com>

March 10, 2004

VIA FEDERAL EXPRESS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

MINOR
AMENDMENT
ORIG AMENDMENT
N/AM

**RE: ANDA 76-633 – Fluticasone Propionate Cream, 0.05%
Minor Amendment – Stability Update – 18 Month Controlled Room Temperature**

Dear Mr. Buehler:

Atrix Laboratories, Inc. (ATRIX) is hereby submitting an updated stability amendment to our unapproved Abbreviated New Drug Application for Fluticasone Propionate Cream, 0.05% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

As stated in the February 19, 2004 Minor Amendment, in answer to the February 04, 2004 FDA correspondence, we are submitting the controlled room temperature 18-month stability data for Exhibit Batch 1567, packaged in 15g, 30g (1567A) and 60g (1567B). The updated stability data sheets for controlled room temperature and — are attached for review. The stability data falls within the specifications filed to support an expiration date of 18 months.

Atrix Laboratories, Inc. considers these final requirements for product approval to be complete. This updated information is submitted for your review and approval.

If there are further concerns or comments please feel free to contact me at (970) 212-4901 or cjones@atrixlabs.com.

Sincerely,

A handwritten signature in cursive script that reads "Cheri Jones".

Cheri Jones, M.S., RAC
Atrix Laboratories, Inc.
Vice President Regulatory Affairs

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MAR 11 2004

000/0001

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



ORIGINAL

Regulatory Affairs
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<http://www.atrixlabs.com>

April 22, 2004

VIA FAX and FEDERAL EXPRESS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

ORIG AMENDMENT

NIAm

**RE: ANDA 76-633 – Fluticasone Propionate Cream, 0.05%
Telephone Amendment - CMC**

Dear Mr. Buehler:

Atrix Laboratories, Inc. (ATRIX) is hereby submitting a telephone amendment to our unapproved Abbreviated New Drug Application for Fluticasone Propionate Cream, 0.05% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

ATRIX is providing the following viscosity methodology requested in a telephone message from Dr. Rashmikant M. Patel earlier today.

The method used to determine the viscosity of the Fluticasone Propionate Cream, 0.05% that Atrix utilizes is USP <911> as a general guideline and _____

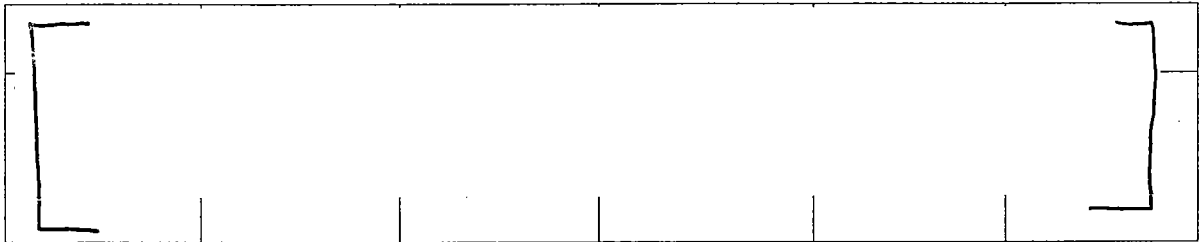
The following information is provided for determination of viscosity for Fluticasone Propionate Cream, 0.05% (calibration of the viscometer assures accuracy and reproducibility of the results) :

Continued on page 2.....

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This information is submitted for your review and approval.

If there are further questions, please feel free to call me at (970) 212-4901. We appreciate your call of today and trust that this clarifies the methodology we utilize.

Sincerely,

ATRIX LABORATORIES, INC.

Cheri Jones, M.S., RAC
Vice President Regulatory Affairs

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



ORIGINAL

Regulatory Affairs
PHONE: (970) 212-4901
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<http://www.atrixlabs.com>

April 27, 2004

FAX and VIA FEDERAL EXPRESS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

**Minor Amendment – Final Approval
Request**

ORIG AMENDMENT
NIAW
XP

**RE: ANDA 76-633 – Fluticasone Propionate Cream, 0.05%
Minor Amendment - Final Approval Request**

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby requesting final approval of the Tentatively Approved Fluticasone Propionate Cream, 0.05% ANDA referenced above as instructed in the Agency Letter of 4/26/04 (attached)

We are enclosing an updated FD&C Act citation to a Paragraph II Patent Certification, effective May 14, 2004.

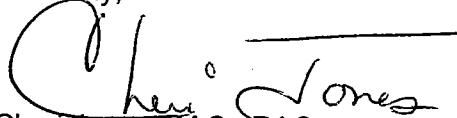
Final Printed Labeling was submitted to the ANDA on February 03, 2004 and is current.

There are no changes to the Chemistry, Manufacturing and Controls (CMC) section of this ANDA since the previous CMC Minor amendment.

If there are further concerns or comments please feel free to contact me at (970) 212-4901 or at cjones@atrixlabs.com.

We look forward to the approval letter for this ANDA product.

Sincerely,


Cheri Jones, M.S., RAC
Atrix Laboratories, Inc.
Vice President, Regulatory Affairs

Enclosure

RECEIVED
APR 28 2004
D/ODER