Approval Package for:

APPLICATION NUMBER:
ANDA 76-633

Name: Fluticasone Propionate Cream, 0.05%

Sponsor: Atrix Laboratories, Inc.

Approval Date: May 14, 2004
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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,

[Signature]
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 5/10/04
HFD-620/S.Liu 5/10/04
HFD-617/W.Pamphile 5/10/04
HFD-613/B.Weitzman 5/10/04
HFD-613/J.Grace 5/10/04

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F/T by
APPROVAL

Robert Furst 5/12/2004

Pending expiration of GSK's exclusivity on 5/10/04
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76-633

TENTATIVE APPROVAL LETTER
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 Cuvate Cream. Since the pediatric data were submitted prior to the November 14, 2003, expiration of the '121 patent, 6-months was be 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 re-activate 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,

[Signature]

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

4/26/2004
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 4/21/04
HFD-613/B.Weitzman 6/17/04
HFD-613/J.Grace 6/18/04

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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
For Dermatologic Use Only —
Not for Ophthalmic Use.

DESCRIPTION: Fluticasone Propionate Cream, 0.05% contains fluticasone propionate (9α,11β-16α,17α,21-trifluoro-11-hydroxy-16-methyl-3-oxo-17-(1H-icosapoxyandrost-14-ene-17-carboxylic acid, S-fluoromethyl ester), a synthetic fluorinated corticosteroid, for topical dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. Chemically, Fluticasone propionate is C_{22}H_{28}F_{4}O_{4}. It has the following structural formula:

\[
\text{CH}_3\text{OCOC}_2\text{H}_5\text{CH}_3\text{OH}\]

Fluticasone propionate has a molecular weight of 506.8. It is a white to off-white powder and is insoluble in water.

Each gram of Fluticasone Propionate Cream contains fluticasone propionate 0.05% in a base of propylene glycol, mineral oil, cetearyl alcohol, Cetyl-20, Cetyl-20, myristate, dioctyl sodium phosphate, citric acid, purified water, and imidazole as preservative.

CLINICAL PHARMACOLOGY: Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by inducing the production of inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their respective precursors, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2. Fluticasone propionate is lipophilic and has a strong affinity for the glucocorticoid receptor. It has weak affinity for the progesterone receptor, and virtually no affinity for the mineralocorticoid, estrogen, or glucocorticoid receptor. The anti-inflammatory and vasoconstrictive potencies of glucocorticoids are related to the half-life of the glucocorticoid-receptor complex. The half-life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.

Studies performed with Fluticasone Propionate Cream indicate that it is in the medium range of potency as compared with other topical corticosteroids.

Pharmacokinetics: Absorption: The activity of Fluticasone Propionate Cream is due to the parent drug. Fluticasone propionate is lipophilic and has a strong affinity for the glucocorticoid receptor. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration.

Topical corticosteroids can be absorbed from normal intact skin, inflammation and/or other disease processes in the skin increase percutaneous absorption.

In a human study of 12 healthy males receiving 12.5 g of 0.05% fluticasone propionate cream applied twice daily for 3 weeks, plasma levels of fluticasone were generally below the level of quantification (0.05 ng/mL). In another study of 6 healthy males administered 25.0 g of 0.025% fluticasone propionate cream under occlusion for 5 days, plasma levels of fluticasone ranged from 0.07 to 0.39 ng/mL.

In an animal study using radiolabeled 0.005% fluticasone propionate cream and ointment preparations, rats received a topical dose of 1 g/kg for a 24-hour period. Recovery of radioactivity was approximately 80% at the end of 7 days. The majority of the dose (72%) was recovered from the surface of the application site. Less than 1% of the dose was recovered in the skin at the application site. Approximately 5% of the dose was absorbed systemically through the skin. Absorption from the skin continued for the duration of the study (7 days), indicating a long retention time at the application site.

Distribution: Following intravenous administration of 1 mg fluticasone propionate in healthy volunteers, the initial disposition phase for fluticasone propionate is released from membrane phospholipids by phospholipase A2. Fluticasone propionate is metabolized in the liver by cytochrome P450 3A4-mediated hydrolysis of the 5-fluoromethyl carboxylate grouping. This transformation occurs in 1 metabolic step to produce the inactive 17α-carboxylic acid metabolite, the only known metabolite detected in man. This metabolite has approximately 2000 times less affinity than the parent drug for the glucocorticoid receptor. Fluticasone propionate may be used with caution in pediatrics patients 3 months of age or older.

Excretion: Following intravenous dose of 1 mg in healthy volunteers, fluticasone propionate showed polyexponential kinetics and had an average terminal half-life of 7.2 hours (range, 3.2 to 11.2 hours).

INDICATIONS AND USAGE: Fluticasone Propionate Cream is a medium-potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Fluticasone Propionate Cream may be used with caution in pediatrics patients 3 months of age or older. 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 under 3 months of age have not been established.

CONTRAINdications: Fluticasone Propionate Cream is contraindicated in those patients with a history of hypersensitivity to any of the components in the preparation.

PRECAUTIONS:

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with potential for gluocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a potent topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary cortisol test.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Inappropriate signs and symptoms of glucocorticoid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Fluticasone propionate cream, 0.05% caused depression of A.M. plasma cortisol levels in 1 of 6 adult patients when used daily for 7 days in patients with psoriasis or eczema involving at least 30% of the body surface. After 2 days of treatment, this patient developed a 60% decrease from pretreatment values in the A.M. plasma cortisol level.

There was some evidence of corresponding decrease in the 24-hour urinary free cortisol levels. The A.M. plasma cortisol level remained slightly depressed for 48 hours but recovered by day 6 of treatment.

Fluticasone propionate cream, 0.05%, caused HPA axis suppression in 4 of 43 pediatric patients, ages 2 and 5 years old, who were treated for 4 weeks covering at least 30% of the body surface area. Follow-up testing 12 days after treatment discontinuation, available for 1 of the 2 patients, demonstrated a normalized HPA axis state.

Fluticasone Propionate Cream is contraindicated in those patients with a history of hypersensitivity to any of the components in the preparation.

Pediatric Use: Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use).

If irritation develops, Fluticasone Propionate Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present at the treatment site, an antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of Fluticasone Propionate Cream should be discontinued until the infection has been adequately controlled.

Fluticasone Propionate Cream should not be used in the presence of preexisting skin atrophy and should not be used where infection is present at the treatment site. Fluticasone Propionate Cream should not be used in the treatment of acne and seborrheic dermatitis.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.

4. Patients should report to their physician any signs of local adverse reaction.

5. Parents of pediatric patients should be advised not to use this medication in the treatment of diaper dermatitis. Fluticasone Propionate Cream should not be applied in the diaper areas as diapers or plastic pants may constitute occlusive dressing (see PRECAUTIONS AND ADMINISTRATION).

6. This medication should not be used on the face, underarms, or groin areas unless directed by a physician.

7. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests: The following tests may be helpful in evaluating patients for HPA axis suppression:

- ACTH stimulation test
- A.M. plasma cortisol test
- Urinary free cortisol test

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two 8-month studies were performed in mice using the carcinogenic potential of fluticasone propionate when given topically (as 0.035% ointment) and orally. No evidence of carcinogenicity was found in either study.

Fluticasone propionate was not mutagenic in the standard Ames test, C. coli fluctuation test, S. cerevisiae gene conversion test, or Chinese Hamster ovary cell assay. It was not clastogenic in mouse micronucleus or cultured human lymphocytes.

In a fertility and general reproductive performance study in rats, fluticasone propionate administered subcutaneously to females at up to 50 mg/kg/day and to males at up to 100 mg/kg per day (after reduced to 50 mg/kg per day) had no effect upon mating performance or fertility. These doses are approximately 15 and 30 times, respectively, the human systemic exposure following use of the recommended human topical dose of fluticasone propionate cream, 0.05%, assuming human percutaneous absorption of approximately 3% and the use in a 70-kg person of 15 g/day.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Fluticasone propionate have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Teratology studies in the mouse.
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 6 years old, who were treated for 4 weeks covering at least 35% of the body surface area. Follow-up testing 10 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, Cushings 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 = 119 pediatric patients ages 1 to 12 years) 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 Fluticasone Propionate Cream 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 2.3%, 1.2%, 1.0%, and 0.6% of patients, respectively.

Two clinical studies compared once-to-twelvedaily 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 2 to 12 years was comparable to the incidence in pediatric patients below 3 months of age.

In 2 vehicle-controlled studies, Fluticasone Propionate Cream applied twice daily for 3 to 4 weeks to an arithmetic mean body surface area of 64% (range, 35% to 95%). The mean morning cortisol levels with standard deviations below treatment (pretreatment mean value = 13.7 ± 6.84 mcg/dL), posttreatment mean value = 30.53 ± 7.20 mcg/dL) and at end treatment (pretreatment mean value = 13.32 ± 6.92 mcg/dL, posttreatment 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 ≥ 44 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; erythematous rash; dry skin; erythema, resolving within 1 month after cessation of Fluticasone Propionate Cream; and telangiectasia, resolving within 3 months after stopping fluticasone propionate cream.

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 in the clinical signs at the end of treatment are shown in Table 4.

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>
<thead>
<tr>
<th>Table 3: Physician's Assessment of Clinical Response</th>
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</thead>
<tbody>
<tr>
<td>Fluticasone Propionate Cream</td>
</tr>
<tr>
<td>Study 1</td>
</tr>
<tr>
<td>Clear</td>
</tr>
<tr>
<td>Excellent</td>
</tr>
<tr>
<td>Good</td>
</tr>
<tr>
<td>Fair</td>
</tr>
<tr>
<td>Poor</td>
</tr>
<tr>
<td>Worsen</td>
</tr>
</tbody>
</table>

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, hypertrichosis, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and milia. Also, there are reports of the development of psustular 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).

Table 4: Clinical Signs: Mean Improvements Over Baseline

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Fluticasone Propionate Cream</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Study 2</td>
<td>Study 1</td>
</tr>
<tr>
<td>Erythema</td>
<td>1.19</td>
<td>1.07</td>
</tr>
<tr>
<td>Thickening</td>
<td>1.22</td>
<td>1.17</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.05</td>
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</tr>
</tbody>
</table>

Table 5: Physician's Assessment of Clinical Response

<table>
<thead>
<tr>
<th>Fluticasone Propionate Cream Once Daily</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleared</td>
<td>35%</td>
<td>28%</td>
</tr>
<tr>
<td>Excellent</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Good</td>
<td>23%</td>
<td>14%</td>
</tr>
<tr>
<td>Fair</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Poor</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>Worsen</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Fluticasone Propionate Cream Once Daily</th>
<th>Fluticasone Propionate Cream Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Study 2</td>
<td>Study 1</td>
</tr>
<tr>
<td>Erythema</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2.1</td>
<td>1.6</td>
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<tr>
<td>Thickening</td>
<td>1.6</td>
<td>1.3</td>
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<tr>
<td>Lichenification</td>
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<tr>
<td>Desquamation</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Crusting</td>
<td>0.6</td>
<td>0.7</td>
</tr>
</tbody>
</table>

HOW SUPPLIED: Fluticasone Propionate Cream, 0.05% is supplied in:
- 15 tubes (NDC 0781-7069-27)
- 30 tubes (NDC 0781-7069-03)
- 60 tubes (NDC 0781-7069-35)

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

Manufactured by:
AstraZeneca, Inc.
Fort Collins, CO 80525

Sandoz Inc.
Broomfield, CO 80020

04417 Rev. 0 1/04
Each gram contains Fluticasone propionate 0.05% in a cream base of propylene glycol, mineral oil, cetyl alcohol, 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.O 1/04
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.

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

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.
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, cetearyl alcohol, Ceteareth-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
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.

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.

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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
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°C and 30°C (36°F 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
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

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-tip onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.
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.

[Signature]

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.
# REVIEW OF PROFESSIONAL LABELING CHECKLIST

<table>
<thead>
<tr>
<th>Applicant's Established Name</th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different name than on acceptance to file letter?</td>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>Are there any other safety concerns?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
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<td><strong>LABELING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).</td>
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<td></td>
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<td></td>
</tr>
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<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is &quot;Jointly Manufactured by...&quot;, statement needed?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
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<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the scoring configuration different than the RLD?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the firm failed to describe the scoring in the HOW SUPPLIED section?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive Ingredients: (FTR: List p. # in application where inactives are listed)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do any of the inactives differ in concentration for this route of administration?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there a discrepancy in inactives between DESCRIPTION and the composition statement?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the term &quot;other ingredients&quot; been used to protect a trade secret? If so, is claim supported?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does USP have labeling recommendations? If any, does ANDA meet them?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insert labeling references a food effect or a no-effect? If so, was a food study done?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>019958</td>
<td>001</td>
<td>4335121</td>
<td>NOV 14,2003</td>
<td></td>
</tr>
<tr>
<td>019958</td>
<td>001</td>
<td>4335121*PED</td>
<td>MAY 14,2004</td>
<td></td>
</tr>
</tbody>
</table>

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]

<table>
<thead>
<tr>
<th>Component</th>
<th>Mfr/DMF</th>
<th>Liner</th>
<th>End Sealant</th>
<th>Resin</th>
<th>Colorant</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 gram Aluminum Tube Cap</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>(Atrix P/N 02070)</td>
<td>DMF #</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 gram Aluminum tube Cap</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>(Atrix P/N 02071)</td>
<td>DMF #</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 gram Aluminum tube Cap</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Atrix P/N 02074)</td>
<td>DMF#</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

Team Leader: John Grace

cc: ANDA: 76-633
DUP/DIVISION FILE
HFD-613/MShin/JGrace (no cc)
v:\firmsam\Atx\tltrs&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: Cevicate® 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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4335121</td>
<td>November 14, 2003</td>
<td>None</td>
<td>None</td>
<td>Paragraph III</td>
<td>Same as</td>
</tr>
<tr>
<td>43351221</td>
<td>May 14, 2004</td>
<td></td>
<td>Paragraph III</td>
<td>Same as</td>
<td></td>
</tr>
</tbody>
</table>

Exclusivity Data – NDA 19-958

<table>
<thead>
<tr>
<th>Code</th>
<th>Reference</th>
<th>Expiration</th>
<th>Labeling Impact</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>There is no unexpired exclusivity for this product.</td>
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## REVIEW OF PROFESSIONAL LABELING CHECKLIST

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**PACKAGING** - See applicant's packaging configuration in FTR

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<td>X</td>
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### Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?

| Are there any other safety concerns? | X |

### LABELING

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</tr>
<tr>
<td><strong>Inactive Ingredients:</strong> (FTR: List p. # in application where inactives are listed)</td>
<td></td>
</tr>
<tr>
<td>Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?</td>
<td>x</td>
</tr>
<tr>
<td>Do any of the inactives differ in concentration for this route of administration?</td>
<td>X</td>
</tr>
<tr>
<td>Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?</td>
<td>X</td>
</tr>
<tr>
<td>Is there a discrepancy in inactives between DESCRIPTION and the composition statement?</td>
<td>X</td>
</tr>
<tr>
<td>Has the term &quot;other ingredients&quot; been used to protect a trade secret? If so, is claim supported?</td>
<td>x</td>
</tr>
<tr>
<td>Failure to list the coloring agents if the composition statement lists e.g., Opocode, Opaspray?</td>
<td>x</td>
</tr>
<tr>
<td>Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?</td>
<td>X</td>
</tr>
<tr>
<td>Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)</td>
<td>x</td>
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<tr>
<td><strong>USP Issues:</strong> (FTR: List USP/NDA/ANDA dispensing/storage recommendations)</td>
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<tr>
<td>Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? [see FTR]</td>
<td>X</td>
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<tr>
<td>Does USP have labeling recommendations? If any, does ANDA meet them?</td>
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<tr>
<td>Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?</td>
<td>X</td>
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<td>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.</td>
<td>X</td>
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<tr>
<td><strong>Bioequivalence Issues:</strong> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)</td>
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</tr>
<tr>
<td>Insert labeling references a food effect or a no-effect? If so, was a food study done?</td>
<td>X</td>
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<tr>
<td>Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.</td>
<td>X</td>
</tr>
<tr>
<td><strong>Patent/Exclusivity Issues:</strong> 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. <strong>See FTR.</strong></td>
<td></td>
</tr>
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</table>

**FOR THE RECORD:**

1. MODEL LABELING: The review was based 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 ADMINISTRATION sections of the labeling.
2. PATENTS/EXCLUSIVITIES

Patent Data

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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 (36°F and 86°F)
- ANDA: Store between 2°C and 30°C (36°F 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: 3/24/00

cc: ANDA: 76-633 – EDR (PDF FILES)
\CDSESUBOGD1\N76633\N_000\2004-02-03
DUP/DIVISION FILE
HFD-613/BWeitzman/JGrace (no cc)
v:\firmsamp\Atrix\Ltrs&rev\76633EDRAP.Labeling.doc
Review
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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<td>31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS</td>
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<td>36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT</td>
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Chemistry Review Data Sheet

1. ANDA 76-633

2. REVIEW #: 1


4. REVIEWER: Benjamin Lim, Ph.D.

5. PREVIOUS DOCUMENTS:

   Previous Documents                           Document Date
   N/A

6. SUBMISSION(S) BEING REVIEWED:

   Submission(s) Reviewed                      Document Date
   Firm:                                        December 31, 2002
   Original Submission                          February 24, 2003
   Amendment (labeling and cGMP letters)       February 26, 2003
   Patent Amendment                             April 17, 2003
   New Correspondence                           

   Agency:                                      February 26, 2003
   Acknowledgement Letter                      
   (Acceptable for Filing: January 2, 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
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.


   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: _X__Rx   ___OTC

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

    _____SPOTS product – Form Completed

    _X__Not a SPOTS product

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

    Cutivate; Fluticasone propionate; S-fluoromethyl-6alpha,9alpha-difluoro-11beta-hydroxy-16alpha-methyl-3-oxo-17alpha-propionyloxandrost-1,4-diene-17beta-carbothioate;
Molecular Formula: $\text{C}_{25}\text{H}_{31}\text{F}_{9}\text{O}_{5}\text{S}$
Molecular Weight: 500.5721
CAS RN: 80474-14-2

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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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)
18. STATUS:

<table>
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<th>CONSULTS/ CMC RELATED REVIEWS</th>
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<td>Microbiology</td>
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<td>Acceptable</td>
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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% in 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, ceteareth-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.
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./

C. CC Block

APPEARS THIS WAY
ON ORIGINAL
Redacted 19 page(s)
of trade secret and/or
confidential commercial
information from

CHEMISTRY REVIEW #1
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
cc: ANDA 76-633
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):
HFD-620/B. Lim, Ph.D. / 6/11/03
HFD-620/S. Liu, Ph.D. / 6/11/03
HFD-617/W. Pamphile, Pharm.D. / 6/11/03

F/T by /

V:\FIRMSAM\ATRX\trs&rev\76633.CR01.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR
ANDA 76-633

Fluticasone Propionate Cream, 0.05%

Atrix Laboratories, Inc.

Benjamin Lim, Ph.D.
Chemistry Division I
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32. LABELING .............................................................................................................19
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34. BIOEQUIVALENCE ..............................................................................................19
35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: ..................................................................................................................19
36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT ..................20

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:

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<td>Original Submission</td>
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<td>February 24, 2003</td>
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<td>February 26, 2003</td>
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6. SUBMISSION(S) BEING REVIEWED:

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7. NAME & ADDRESS OF APPLICANT:

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

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    ____SPOTS product – Form Completed
    _X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
    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_{3}O_{5}S
    Molecular Weight: 500.5721
    CAS RN: 80474-14-2
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

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

B. Other Documents:

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18. STATUS:

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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: Minor Amendment

Note: The Section B of the last NA letter has been acknowledged by the applicant.
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 $+32^\circ$ and $+36^\circ$ (0.5% w/v in dichloromethane, $t = 25^\circ$C and 589.3 nm).

Drug Product
Fluticasone Propionate Cream, 0.05% in 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 A$_2$ 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.
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./ 2/1/04
W. Pamphile, Pharm.D./ 2/1/04

2/2/04

C. CC Block
Redacted 10 page(s)

of trade secret and/or confidential commercial information from

CHEMISTRY REVIEW 2
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.

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,

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

2/2/04
cc: ANDA 76-633
    ANDA DUP
    DIV FILE
    Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D. / 2/2/04
HFD-620/S. Liu, Ph.D. / 2/2/04
HFD-617/W. Pamphile, Pharm.D. / 2/2/04

F/T by / wp

V:\FIRMSAM\ATRIX\msgs\rev\76633.CR02.rev.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR
ANDA 76-633

Fluticasone Propionate Cream, 0.05%

Atrix Laboratories, Inc.

Benjamin Lim, Ph.D.
Chemistry Division I
# Table of Contents

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   C. CC Block .................................................................................................................... 9

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21. FACILITIES .................................................................................................................. 12

22. SYNTHESIS .................................................................................................................. 12

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<td>31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS</td>
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<td>35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION</td>
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Chemistry Review Data Sheet

1. ANDA 76-633

2. REVIEW #: 3

3. REVIEW DATE: April 16, 2004

4. REVIEWER: Benjamin Lim, Ph.D.

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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: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed
    _X__ Not a SPOTS product

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

    Cutivate; Fluticasone propionate; S-fluoromethyl-6alpha,9alpha-difluoro-11beta-hydroxy-
    16alpha-methyl-3-oxo-17alpha-propionyloxyandrosta-1,4-diene-17beta-carbothioate;
    
    Molecular Formula: C_{23}H_{31}F_{3}O_{5}S
    Molecular Weight: 500.5721
    CAS RN: 80474-14-2
17. RELATED/SUPPORTING DOCUMENTS:

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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:

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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

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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, $t = 25^\circ$C and 589.3 nm).

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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.
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./

4/16/04

4/16/04

4/16/04

C. CC Block

APPEARS THIS WAY ON ORIGINAL
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of trade secret and/or
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.


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

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D./  4/16/04
HFD-620/S. Liu, Ph.D./  4/21/04
HFD-617/W. Pamphile, Pharm.D./  4/21/04

F/T by

V:\FIRMSAM\ATRIX\lttrs&rev\76633.CR03.doc

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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    B. Endorsement Block .................................................. 9
    C. CC Block ............................................................. 9

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1. ANDA 76-633

2. REVIEW #: 4

3. REVIEW DATE: May 4, 2004

4. REVIEWER: Benjamin Lim, Ph.D.

5. PREVIOUS DOCUMENTS:

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|CMC Deficiency Letter #2                                | June 24, 2003          |
|Telephone call from Dr. Patel                          | February 4, 2004       |
|Tentative Approval Letter                               | April 22, 2004         |
|                                                        | April 26, 2004         |

6. SUBMISSION(S) BEING REVIEWED:

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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-6alpha,9alpha-difluoro-11beta-hydroxy-16alpha-methyl-3-oxo-17alpha-propionateandrosta-1,4-diene-17beta-carbothioate;

     Molecular Formula: \( C_{25}H_{31}F_3O_5S \)
CHEMISTRY REVIEW

Chemistry Assessment Section

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

17. RELATED/SUPPORTING DOCUMENTS:

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Other codes indicate why the DMF was not reviewed, as follows:
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3 – Reviewed previously and no revision since last review
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B. Other Documents:
18. STATUS:

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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: Minor Amendment
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)

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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. Panophile, Pharm.D./

C. CC Block

APPEARS THIS WAY ON ORIGINAL
Redacted 4 page(s)
of trade secret and/or
confidential commercial
information from

CHEMISTRY REVIEW #4
cc: ANDA 76-633
    ANDA DUP
    DIV FILE
    Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D./5/10/04
HFD-620/S. Liu, Ph.D./5/10/04
HFD-617/W. Pamphile, Pharm.D./5/10/04

F/T by

V:\FIRMSAM\ATRX\lttrs&rev\76633.CR04.doc

TYPE OF LETTER: APPROVABLE

APPEARS THIS WAY
ON ORIGINAL
APPLICATION NUMBER:
ANDA 76-633

BIOEQUIVALENCE REVIEW(S)
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® 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® 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\textsuperscript{R} (fluticasone propionate) cream, 0.05% to be used to estimate the ED\textsubscript{50} 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\textsuperscript{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\textsuperscript{R} (fluticasone propionate cream) 0.05% cream, Lot #1C299, Expiration Date 03/04.

Randomization: Cutivate\textsuperscript{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\textsuperscript{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\textsuperscript{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:

<table>
<thead>
<tr>
<th>Method</th>
<th>Parameter</th>
<th>Firm (A)</th>
<th>Reviewer (B) A/B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChromaMeter</td>
<td>$\text{ED}_{50} \text{ (min)}$</td>
<td>61.7</td>
<td>61.1</td>
</tr>
<tr>
<td></td>
<td>$E_{\text{max}}$ (a scale units*min)</td>
<td>15.3</td>
<td>12.4</td>
</tr>
</tbody>
</table>

$\text{ED}_{50}$ based on the reviewer calculations is approximately 61 minutes. The firm employed an $\text{ED}_{50}$ 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 $\text{ED}_{50}$ 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, CutivateR (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:

<table>
<thead>
<tr>
<th>AUEC&lt;sub&gt;0-24&lt;/sub&gt;</th>
<th>Test/Ref</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>11.6</td>
<td>12.0</td>
<td>0.968</td>
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</table>

The 90% CI for AUEC<sub>0-24</sub> 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.

<table>
<thead>
<tr>
<th>Components</th>
<th>Function</th>
<th>Formulation (%&lt;sub&gt;w/w&lt;/sub&gt;)</th>
<th>ANDA Batch</th>
<th>Commercial Batch</th>
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</thead>
<tbody>
<tr>
<td>Fluticasone propionate</td>
<td>Active</td>
<td>0.05</td>
<td>___*</td>
<td>___:*</td>
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<tr>
<td>Propylene glycol, USP</td>
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<td>Sodium phosphate dibasic, USP</td>
<td></td>
<td></td>
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<tr>
<td>Citric acid, USP</td>
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</tr>
<tr>
<td>Imidurea, NF</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineral oil, USP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isopropyl myristate, NF</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cetostearyl alcohol, NF</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Ceteth-20</td>
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</tr>
<tr>
<td>Purified water, USP</td>
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<td></td>
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</table>

*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 (Cultivate® Cream 0.05%) based on the OGD guidance. Based on a population fitting technique of the chromaMeter dose-response data, an ED<sub>50</sub> of approximately 60 minutes was calculated. For the pivotal bioequivalence study, the sponsor used D<sub>1</sub>, ED<sub>50</sub> and D<sub>2</sub> 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 INITIALLED
FT INITIALLED GJP SINGH

11-19-03

Concur: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Mmakary/ 11-17-03, 76633N1202.doc
cc: ANDA #76-633, original, HFD-658 (Makary), Drug File, Division File.
ENDORSEMENTS: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh
HFD-650/ D. Conner

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
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
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:

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<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>C.V.%</th>
<th>Distrib.</th>
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<tbody>
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Sigma = 82.21883

Nb of EM iterations: 4

Final population parameter estimates:

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<th>Std. Dev.</th>
<th>C.V.%</th>
<th>Distrib.</th>
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Sigma = 83.36902
Maximum Likelihood = -452.0931
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Individual parameters

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N: 15. 15. 15.
Mean: 85.97716 15.73847 | 8.
Max: 218.9537 46.8544 | 15.
SD: 65.89179 13.16226 | 4.47214
Var: 4341.72777 173.24509 | 20.
C.V.: 76.63871 83.63115 | 55.9017
<table>
<thead>
<tr>
<th>GJP Singh</th>
<th>ANDA 76-633</th>
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<tbody>
<tr>
<td>DBE/OGD</td>
<td>Chrom, DETECT</td>
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<tr>
<td>Date</td>
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<tr>
<td>Reviewer:</td>
<td>M. Makary</td>
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<tr>
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<td>(%) -48</td>
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<tr>
<td>-CINT</td>
<td>0.8225</td>
</tr>
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</table>

**90% CI:** 115.48 82.25
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

<table>
<thead>
<tr>
<th>Dose Duration (Min)</th>
<th>AUEC Unoccluded (A)</th>
<th>AUEC Occluded (B)</th>
<th>B/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>-1.1</td>
<td>3.9</td>
<td>-3.55</td>
</tr>
<tr>
<td>30</td>
<td>4</td>
<td>8.1</td>
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<tr>
<td>60</td>
<td>6</td>
<td>7.8</td>
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<tr>
<td>120</td>
<td>3.2</td>
<td>5.6</td>
<td>1.75</td>
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<td>180</td>
<td>7.1</td>
<td>12.8</td>
<td>1.80</td>
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<tr>
<td>240</td>
<td>0</td>
<td>12.7</td>
<td>&gt; 12.7</td>
</tr>
<tr>
<td>360</td>
<td>2.8</td>
<td>12.3</td>
<td>4.39</td>
</tr>
</tbody>
</table>

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  
Date: 1/22/04
Moheb H. Makary, Ph.D.  
Review Branch III  
Division of Bioequivalence

RD INITIALLIED  
FT INITIALLIED GJP SINGH  
Date 1/22/04

Concur: Dale P. Conner, Pharm.D.  
Date: 1/22/04  
Director  
Division of Bioequivalence

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

[Signature]

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\ultrs\rev176633STA1203.doc
Printed in final on 1/22/04

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader G. Singh
HFD-650/ D. Conner

BIOEQUIVALENCE - ACCEPTABLE submission date: December 5, 2003

1. Study Amendment (STA) Strengths: 0.05%
   Clinical: ____________________________ Outcome: AC

Outcome Decisions: AC
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: □ □
ANALYTICAL SITE: N/A

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

DSI INSPECTION STATUS

<table>
<thead>
<tr>
<th>Inspection needed: No.</th>
<th>Inspection status:</th>
<th>Inspection results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Generic No.</td>
<td>Inspection requested: (date)</td>
<td></td>
</tr>
<tr>
<td>New facility</td>
<td>Inspection completed: (date)</td>
<td></td>
</tr>
<tr>
<td>For cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PRIMARY REVIEWER: Moheb H. Makary, Ph.D.
SIGNATURE: ________________
DATE: 1/22/04

TEAM LEADER: G. Singh, Ph.D.
SIGNATURE: ________________
DATE: 1-22-04

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
SIGNATURE: ________________
DATE: 1/22/04
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76-633

ADMINISTRATIVE DOCUMENTS
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

(Handwritten note: 'FYI was inserted that pediatric exclusivity has been granted & that firms should provide an amendment which recognizes an additional 6 months of exclusivity. That will attach to patent #4335121 & extend its expiration until 05/14/03. Signed: March 2003')
**APPLICATION REASSIGNMENT AUTHORIZATION FORM**
**OFFICE OF GENERIC DRUGS**

<table>
<thead>
<tr>
<th>ANDA/AADA#</th>
<th>DRUG</th>
<th>FIRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>76-633</td>
<td>Fluticasone Propionate Cream</td>
<td>Atrix</td>
</tr>
</tbody>
</table>

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)**

---

**BRANCH SUPERVISOR (SIGNATURE):** ____________________________ **DATE:** __________

**CHEMISTRY/BIOEQUIVALENCE DIVISION DIRECTOR (SIGNATURE):** ____________________________ **DATE:** __________

---

**CONCUR: **__ **NOT CONCUR: **__

---

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

---

**Signature:** __________ **Date:** __________
**Record of Telephone Conversation**

Reference is made to chemistry deficiency letter dated June 24, 2003. The firm wanted clarification on the following deficiencies:

3. Please add limits regarding ____________________________
   ____________________________________________

Atrix: Are you asking for the ____________________________? Also, should we ask the manufacturer to provide the test?

FDA: Yes (to both questions).

6. Regarding container/closure system, we have the following comments:
   
   b. Please provide test results for __________________________ of the tube. Test method should be provided.

Atrix: Can we use information provided by the manufacturer of the tubes?

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.

7. Regarding the bulk in-process control specifications, we have the following comments:
   
   a. Please add limits for ______ based on a validated method.

   b. Please add a procedure for ______ before packaging.

Atrix: Please explain why you want us to add limits for the ______ test.

FDA: The USP method is acceptable

Atrix: It's assumed that __________________________

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.

---

**Date:**

July 28, 2003

**Anda Number:**

76-633

**Telecon Initiated by Sponsor**

**Product Name:** Fluticasone Propionate Cream, 0.05%

**Firm Name:** Atrix Laboratories, Inc.

**Firm Representatives:**
Lynn Hansen
Cheri Jones

**Telephone Number:**

970-482-5868

**Fda Representatives**

Shing Liu, Ph.D.
Benjamin Lim, Ph.D.
Wanda Pamphile, Pharm.D.

**Signatures:**

Shing Liu
Benjamin Lim
Wanda Pamphile

---

Orig: ANDA 76-633
Cc: Division File
    Chem. I Telecon Binder
V:\FIRMSAM\ATRIX\Telecon\76633.doc
8. Regarding the finished drug product specifications, we have the following comments:

   a. Please add limits for ______ based on a validated method.

   b. Please add limits for ______ based on validated methods.

Atrix: The validated method is a USP method, and we will mention that in our response.

FDA: That will be fine.

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.

Atrix: We spoke to Martin Shimer sometime ago and we were told that we can use alternate accelerated conditions.

FDA: We will not accept ______ it is not in the FDA guidelines.

Atrix: However, we ______

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.
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: Martin Shimer
Chief, Reg. Support Branch

DRAFT Package
Date: 4-16-04
Initials: WDF

FINAL Package
Date: 4-21-04
Initials: WDF

1. Contains GDEA certification: Yes [☑] No [ ]
   (required if sub after 6/1/92)

   Patent/Exclusivity Certification: Yes [☑] No [ ]

   If Para. IV Certification- did applicant:
   Notify patent holder/NDA holder Yes [☑] No [ ]

   Was applicant sued w/in 45 days: Yes [☑] No [ ]

   Has case been settled: Yes [☑] No [ ]

   Generic Drugs Exclusivity for each strength: Yes [☑] No [ ]

   Eligible For TAI: [☑]

   Pediatric Exclusivity
   Previous granted

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

Original Rec'd date: 12-31-02
Date Acceptable for Filing: 1-2-03
Patent Certification (type): CR
Date Patent/Exclus.exp. expires: 6-14-04

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 [ ]
Acceptable Bio reviews tabbed Yes [☑] No [ ]
Suitability Petition/Pediatric Waiver: Interim Dissol. Specs in AP Ltr: Yes [☑]

Previously reviewed and tentatively approved □ Date □
Previously reviewed and CGMP def./NA Minor issued □ Date □

3. Div. Dir./Deputy Dir.
Chemistry Div. I

Comments:
The cmc section is satisfactory for th

Date: 4/23/04
Initials: [☑]

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

NA. ANDA 76-300 (Altana) was tentatively approved on 01/03 for Fluticasone Ointment.
KLD = Ciltivate Cream 0.05%
GSK

6. Peter Rickman
   Director, DLPS
   Para IV Patent Cert: Yes ☐ No ☑ Pending Legal Action: Yes ☐ No ☑ Petition for Review: No
   Comments: Acceptable CDS dated 3/10/03 (updated 4/26/04) No ADR. Robert noted biological assays, no toxicity, and acceptable 12/8/04. Study performed by Thistle Valley has an acceptable CDS, inspectional history of GSK shows bioequivalence results, in final print 3/24/06. CDS found acceptable 4/10/04. Methods validation will not be requested - does not meet current criteria.

6. Robert L. West
   Deputy Director, OGD
   Para IV Patent Cert: Yes ☐ No ☑ Pending Legal Action: Yes ☐ No ☑ Petition for Review: Yes ☐ No
   Comments: On 14/03/04 made a paragraph III certification to the Tentative ANDA that was due to expire on 11/14/03. This patent was effectively extended until 11/14/03 upon the granting of pediatric exclusivity to GSK for Ciltivate (Pat Neuro).

   This ANDA may be granted a tentative approval (pending the expiration of GSK's pediatric exclusivity on 11/14/04).

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

8. Project Manager, Team Wanda Pamphile
   Review Support Branch 6
   Date PETS checked for first generic drug (just prior to notification to firm) ☑
   Applicant notification:
   11/14/03 Time notified of approval by phone 11/14/03 Time approval letter faxed
   FDA Notification:
   11/14/03 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
   11/14/03 Date Approval letter copied to \CED014\DRUGAPP\ directory.
OGD APPROVAL ROUTING SUMMARY

ANDA # 76-633
Applicant Atrix Laboratories, Inc.
Drug Fluticasone Propionate Cream
Strength(s) 0.05%

PROVAL ✗ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:
1. Martin Shimer
Chief, Reg. Support Branch

Contains GOEA certification: Yes ☑ No ☐ Determin. of Involvement? Yes ☑ No ☐
(required if sub after 6/1/92)

Patent/Exclusivity Certification: Yes ☑ No ☐ Pediatric Exclusivity System
If Para. IV Certification- did applicant 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: 5/14/2001
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☑ No ☐
Type of Letter: ☐
Comments:

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

Original Rec'd date 12-31-02
Date Acceptable for Filing 1-2-03 ✓
Patent Certification (type) JT
Date Patent/Exclus.expires N/A
Citizens' Petition/Legal Case Yes ☑ No ☐ Date of Sterility Assur. App. N/A
(If YES, attach email from PM to CP coord.) Methods Val. Samples Pending Yes ☑ No ☑
First Generic Yes ☑ No ☑
Acceptable Bio reviews tabbed 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 9-26-04
Previously reviewed and CGMP def. /NA Minor issued ☐

Comments:

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

Comments: N/A

4. Div. Dir./Deputy Dir.
Chemistry Div. I ☐ OR ☑

Comments:

No Change in CMS since TA Remain satisfactory for final approval.
6. Vacant
Deputy Dir., DLPS

GLAXOSMITHKLINE
NDA 19-958

Para.IV Patent Cert: Yes □ No ☑ Pending Legal Action: Yes □ No ☑ Petition: Yes No ☑
Comments: Acceptable EFS date is 9/3/04 (checked 9/21/04). No OAM alerts noted
Robert L. West
Deputy Director, OGD
Para.IV Patent Cert: Yes □ No ☑ Pending Legal Action: Yes □ No ☑ Petition: Yes No ☑
Comments: At same time a paragraph III certification to the ‘131 patent that expired on 11/14/03. However, prior to the expiration of the ‘131 patent, GSK was awarded pediatric exclusivity for the RUL Caticlate. This effectively extended the patent until 6/14/04. 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:
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 VP

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.
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

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,

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

RECEIVED
JAN 02 2003
OGD / CDER
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

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
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

c: 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 date
HFD-615/MShimer, CSO date

Word File V:\Firmsam\Atrix\Ltrs&rev\76633.ack
F/T EEH 02/25/03
ANDA Acknowledgment Letter!
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

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.

ATTN: Kathy Corso

FROM: Wanda Pamphile

TEL: 970-212-4884

FAX: 970-482-9734

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.
Redacted __ page(s)
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,

[Signature]

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

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
Ms. Wanda Pamphilie  
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. Pamphilie:

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 O'Hansen  
Atrix Laboratories, Inc.  
Regulatory Affairs
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 ______
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).
Please contact me at (970) 212-4884 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
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

VIA FEDERAL EXPRESS

MINOR AMENDMENT

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  

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.
Redacted 6 page(s) of trade secret and/or confidential commercial information from 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,

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)

APPLICANT: Atrix Laboratories, Inc.
ATTN: Cheri Jones
FROM: Beth Fritsch

TEL: 970-212-4901
FAX: 970-482-9734
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:

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.
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
VIA FEDERAL EXPRESS

BIOEQUIVALENCY AMENDMENT

December 5, 2003

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 _____________________________.
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
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.
VIA FEDERAL EXPRESS

UNSOLICITED MINOR AMENDMENT

February 03, 2004

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.

RECEIVED
FEB 0 4 2004
OGD/CDER
Redacted ___ page(s)

of trade secret and/or

confidential commercial

information from

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.

[Signature]

Cheri Jones, M.S., RAC
Vice President Regulatory Affairs
VIA FEDERAL EXPRESS

AMENDMENT TO PENDING ANDA

February 03, 2004

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

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.

RECEIVED
FEB 04 2004
OGD/CDER
Sincerely,

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)

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 (____ 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.
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
February 19, 2004

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

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.
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
March 10, 2004

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

VIA FEDERAL EXPRESS

MINOR AMENDMENT
ORIG AMENDMENT
N/A M

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,

Cheri Jones, M.S., RAC
Atrix Laboratories, Inc.
Vice President Regulatory Affairs
April 22, 2004

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

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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APR 2 3 2004  
OGD / GDER
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
April 27, 2004

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

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 previouse 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