CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-152

PHARMACOLOGY REVIEW

Memorandum

To: NDA 21-152
From: Barbara Hill, Ph.D.
Through: Paul Brown, Ph.D., Pharmacology/Toxicology Supervisor
Re:

Submission dates:	2-1-05
Supplement No.:	000 AZ
Submission type:	Response to Approvable letter
Drug:	Cutivate (fluticasone propionate) lotion, 0.05%
Drug class:	Corticosteroid, anti-inflammatory
Indication:	Corticosteroid responsive dermatoses
Sponsor:	GlaxoSmithKline, Parsippany, NJ

Review date: February 28, 2005

Clinical formulation:

Each gram of CUTIVATE Lotion contains 0.5 mg fluticasone propionate in a base of cetostearyl alcohol, isopropyl myristate, propylene glycol, cetomacrogol 1000, dimethicone 360, citric acid, sodium citrate, and purified water, with imidurea, methylparaben, and propylparaben as preservatives.

Related INDs/NDAs:

1) IND 28,635 (Cutivate ointment; corticosteroid responsive dermatoses; HFD-540)
2) IND 28,636 (Fluticasone propionate aqueous nasal spray; seasonal or perennial rhinitis and corticosteroid responsive dermatoses; HFD-570)
3) IND 28,765 (Cutivate cream; Corticosteroid-responsive dermatoses; HFD-540)
4) IND 29,039 (Fluticasone propionate inhaler; chronic reversible obstructive disease; HFD-570)
5) IND 40,142 (Fluticasone propionate rotadisk; anti-asthmatic; HFD-570)
6) IND 53,502 (Fluticasone propionate/GR106642X; inhalational maintenance treatment of asthma; HFD-570)
7) IND 54,894 (Cutivate lotion; corticosteroid responsive dermatoses; HFD-540)

1) NDA 19-957 (Cutivate ointment; corticosteroid responsive dermatoses, HFD-540, approved 12-14-90)
2) NDA 19-958 (Cutivate cream; corticosteroid responsive dermatoses, HFD-540, approved 12-18-90)
3) NDA 20-121 (Flonase nasal spray; relief of the symptoms of seasonal or perennial rhinitis, HFD-570, approved 10-19-94)
4) NDA 20-548 (Flovent aerosol; maintenance treatment of bronchial asthma, HFD-570, approved 3-27-96)
5) NDA 20-549 (Flovent/Rotadisk inhalation powder; maintenance treatment of bronchial asthma, HFD-570, approved 11-7-97)

6) NDA 21-077 (Advair diskus {salmeterol/fluticasone propionate}; maintenance treatment of asthma; HFD-570; approved 8-24-00)

Introduction:

Cutivate Ointment, 0.005%, and Cutivate Cream, 0.05%, were approved in December 1990 for the treatment of corticosteroid responsive dermatoses. The sponsor has developed a line extension Cutivate topical drug product (lotion formulation) for the treatment of corticosteriod responsive dermatoses. The Cutivate lotion NDA (NDA 21-152) was resubmitted on March 12, 2004. After review of the application, an approvable letter was sent to the sponsor on January 12, 2005. Two aspects of the approvable letter for Cutivate lotion related to nonclinical Pharmacology/Toxicology issues. The two nonclinical issues are reproduced below.

1. Initiate labeling discussions with the Division to address the outstanding labeling issues, identified in the attached draft labeling. The Division acknowledges your January 6, 2005, correspondence in which you state your commitment to further labeling negotiations with the Division.

4. The Division has determined that the data submitted to NDA 21-152 to support a waiver for a study to determine the photoco-carcinogenic potential of Cutivate lotion is not adequate. It is requested that the Sponsor submit their plan for conduct of a study to determine the photoco-carcinogenic potential of Cutivate lotion. The applicant is referred to the guidance document titled "Guidance for Industry – Photosafety Testing" published in May, 2003 for assistance in determining an appropriate study design.

The current submission addresses the issues relayed to the sponsor in the approvable letter. The sponsor's response to the Pharmacology/Toxicology (nonclinical) issues will be evaluated in this review. A team meeting was conducted for this submission on February 14, 2005 to determine if a complete response to all of the issues raised in the approvable letter had been included in the submission. It was determined that a complete response had been submitted and that this submission qualified for a 2 month review timeline.

Sponsor's response to nonclinical label recommendations:

The recommended changes for the nonclinical portions of the Cutivate lotion label that were relayed to the sponsor in the approvable letter are provided below. Recommended additions are provided in <u>underlined</u> text and recommended deletions are provided in ~~strikeout~~ text.

Note: The multiples of human exposure provided in the label below were calculated based on assuming 100% systemic absorption of the maximum daily dose of fluticasone propionate lotion, 0.05% (25 g/day). The actual calculations are provided in the original Pharmacology/Toxicology review for the resubmission of the NDA. All of the multiples of human exposure for the nonclinical studies that were incorporated into the label are less than one when assuming 100% systemic absorption.

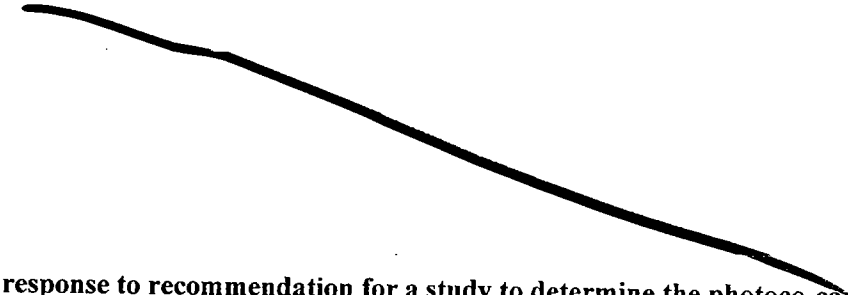
4 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Pharm/Tox-*1



Sponsor's response to recommendation for a study to determine the photoco-carcinogenic potential of Cutivate lotion:

It was determined that the data submitted to NDA 21-152 to support a waiver for a study to determine the photoco-carcinogenic potential of Cutivate lotion is not adequate. The Division requested in the approvable letter that the Sponsor submit their plan for conduct of a study to determine the photoco-carcinogenic potential of Cutivate lotion. The Sponsor states in the current submission that they consider the data submitted to NDA 21-152 to be sufficient to appropriately evaluate the photoco-carcinogenic potential of Cutivate lotion. In addition, the Sponsor states that they consider photocarcinogenicity testing to be unnecessary. The sponsor also states that they consider the sentence that the division added to the Cutivate lotion label which states "No studies were conducted to determine the photoco-carcinogenic potential of CUTIVATE lotion" to be appropriate.

The Sponsor did not provide any new information to address the photoco-carcinogenic potential of Cutivate lotion in the current submission. The Sponsor still maintains that the information that was previously submitted should be adequate to grant a waiver for conduct of a study to determine the photoco-carcinogenic potential of Cutivate lotion. There were a number of reasons why it was determined that the data submitted was not adequate to support this waiver request. A summary of these reasons will be provided below. The reader is referred to the original NDA review if additional detail is necessary.

The Sponsor states that Cutivate lotion is not photoreactive (does not demonstrate any appreciable absorption in the range). This is not an acceptable reason to grant a waiver for the study because there are other mechanisms besides direct photoreactivity that can contribute to an enhanced photoco-carcinogenic risk (i.e., enhanced UV exposure, thinning of the skin, etc).

In the original NDA submission, the sponsor included five literature references to support their belief that published data indicate that corticosteroids in general elicit a photoprotective effect by inhibiting the induction of UV-induced skin tumors or by down-regulating mediators of inflammation and tumor promotion. The sponsor reiterates this point in the current submission. It was determined that the published data submitted to support the Sponsor's viewpoint was not adequate. Only a few corticosteroids were tested in the studies referenced in the submitted literature. It is not possible to designate a class effect based on the limited data set. Not much information was provided about the UV lamps and filters used in the studies described in the

submitted literature references. The lamps used in these studies may have been sunlamps that had UVC present (with inadequate filtering). A drug that absorbs UVC might appear to be protective in these studies versus UVC exposure. In addition, an important question that is not addressed in these studies is whether any "protective" effect (which all anti-inflammatory drugs may possess) could be outweighed by optical effects. One reference study was conducted with hydrocortisone dissolved in propylene glycol, which does not mimic the composition of the Cutivate lotion vehicle. It is not clear what is the composition of the emollient vehicle used in another reference study. Results from photoco-carcinogenesis studies conducted in hairless mice to support the safety of other topical drug products have demonstrated that the optical properties of the vehicle (i.e., enhance the UV exposure to the skin) frequently is the predominant effect for enhancement of photoco-carcinogenesis. It appears that the optical effect may be stronger than any additional immunosuppressive effect based on the results of these studies. Therefore, it would be important to determine the photoco-carcinogenic potential of Cutivate lotion.

Another part of the Sponsor's argument for granting a waiver for the study to determine the photoco-carcinogenic potential of Cutivate lotion is related to submitted clinical data in the original NDA submission. The Sponsor claims that the submitted clinical data demonstrate that the potential degree of skin thinning resulting from topical application of fluticasone proprionate is not significant and is comparable or less than that of hydrocortisone. The skin thinning assessed in the clinical studies after administration of fluticasone propionate 0.5% cream may not be an appropriate marker for assessing the photoco-carcinogenic potential of Cutivate lotion. The thinning of the skin measured in the referenced clinical studies measured the thickness of collagen, but not of the stratum corneum. The "Photosafety testing" guidance document refers to measurement of thinning of the "protective" layers of the skin (e.g., the stratum corneum). Therefore, measurement of thinning of the skin by measurement of collagen thickness is not an appropriate marker for photoco-carcinogenic potential.

The sponsor states in the current submission that since their position differs from that of the Agency, they request a teleconference to discuss the necessity of the photoco-carcinogenicity study in light of the available data. In summary, the sponsor did not provide any new information in this submission to support their request for a waiver for a study to determine the photoco-carcinogenic potential of Cutivate lotion. Therefore, it is my opinion that a teleconference with the sponsor may not be productive. It is recommended that the rationale for not granting a waiver for the conduct of a photoco-carcinogenic study (provided in the following section) be relayed to the sponsor via fax. Perhaps this will be adequate to allow the sponsor to understand the Division's viewpoint for this issue.

Recommendations:

[redacted]

External (to be relayed to the sponsor):

It is recommended that the following be relayed to the sponsor for NDA 21-152, Serial# 000 AZ, submitted on February 1, 2005.

1) The Sponsor's proposal to calculate the multiples of human exposure values for the Cutivate lotion label assuming 3% percutaneous absorption of Cutivate lotion is not acceptable. In the absence of AUC data, the Division's policy is to calculate the multiples of human exposure values for topical drug product labels assuming 100% percutaneous absorption. Therefore, the Division recommends that the Sponsor accept the Division's original wording for the nonclinical portions of the Cutivate label relayed to them in the NDA Approvable Letter sent on January 12, 2005.

2) The Division notes that the Sponsor did not submit any new data in this submission to support their request for a waiver for conduct of a study to determine the photoco-carcinogenic potential of Cutivate lotion. Therefore, the Sponsor is relying on the data that was included in the original NDA 21-152 submission (date of submission – March 12, 2004). The Division previously relayed to the sponsor in the NDA Approvable Letter for NDA 21-152 (dated January 12, 2005) that the Division has determined that the data submitted to NDA 21-152 to support a waiver for a study to determine the photoco-carcinogenic potential of Cutivate lotion is not adequate. This determination has not changed since no new data has been submitted to the Division. There are a number of reasons why the data was determined not to be adequate to grant the waiver. A few of these reasons are provided below.

   a) The lack of photoreactivity of Cutivate lotion (does not demonstrate any appreciable absorption in the [redacted] range), is not an acceptable reason to grant a waiver for the study because there are other mechanisms besides direct photoreactivity that can contribute to an enhanced photoco-carcinogenic risk (i.e., enhanced UV exposure, thinning of the skin, etc).

   b) In the original NDA submission, the sponsor included a few literature references to support their belief that published data indicate that corticosteroids in general elicit a photoprotective effect by inhibiting the induction of UV-induced skin tumors. It was determined that the published data submitted to support the Sponsor's viewpoint was not adequate. Only a few corticosteroids were tested in the studies referenced in the submitted literature. It is not possible to designate a class effect based on the limited data set. Not much information was provided about the UV lamps and filters used in the studies described in the submitted literature references. The lamps used in these

studies may have been sunlamps that had UVC present (with inadequate filtering). A drug that absorbs UVC might appear to be protective in these studies versus UVC exposure. In addition, an important question that is not addressed in these studies is whether any "protective" effect (which all anti-inflammatory drugs may possess) could be outweighed by optical effects. One literature reference study was conducted with hydrocortisone dissolved in propylene glycol, which does not mimic the composition of the Cutivate lotion vehicle. The composition of the emollient vehicle used in another reference study is not clear. Results from photoco-carcinogenesis studies conducted in hairless mice to support the safety of other topical drug products have demonstrated that the optical properties of the vehicle (i.e., enhance the UV exposure to the skin) frequently is the predominant effect for enhancement of photoco-carcinogenesis. Therefore, it would be important to determine the photoco-carcinogenic potential of Cutivate lotion.

c) The Sponsor claims that the clinical data submitted in the original NDA demonstrate that the potential degree of skin thinning resulting from topical application of fluticasone proprionate is not significant and is comparable or less than that of hydrocortisone. The skin thinning assessed in the clinical studies after administration of fluticasone propionate 0.5% cream may not be an appropriate marker for assessing the photoco-carcinogenic potential of Cutivate lotion. The thinning of the skin measured in the referenced clinical studies measured the thickness of collagen, but not of the stratum corneum. The "Photosafety testing" guidance document refers to measurement of thinning of the "protective" layers of the skin (e.g., the stratum corneum). Therefore, measurement of thinning of the skin by measurement of collagen thickness is not an appropriate marker for photoco-carcinogenic potential.

3) In summary, the Division has determined that the data submitted to NDA 21-152 to support a waiver for a study to determine the photoco-carcinogenic potential of Cutivate lotion is not adequate. It is requested that the Sponsor submit their plan for conduct of a study to determine the photoco-carcinogenic potential of Cutivate lotion. The applicant is referred to the guidance document titled "Guidance for Industry – Photosafety Testing" published in May, 2003 for assistance in determining an appropriate study design.

cc:
HFD-540/DIV DIR/WILKIN
HFD-540/ PHARM SUP/BROWN
HFD-540/PHARM/HILL
HFD-540/MO/COOK
HFD-540/CHEM/FENSELAU
HFD-540/PM/WRIGHT

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Barbara Hill
3/14/05 11:52:04 AM
PHARMACOLOGIST

Paul Brown
3/14/05 01:18:41 PM
PHARMACOLOGIST

Review for
1/12/05 A & Ltr

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-152**
SERIAL NUMBER:	**000 and BZ**
DATE RECEIVED BY CENTER:	**3/12/04 and 7/23/04**
PRODUCT:	**Cutivate lotion, 0.05%**
INTENDED CLINICAL POPULATION:	**Corticosteroid responsive dermatoses**
SPONSOR:	**GlaxoSmithKline**
DOCUMENTS REVIEWED:	**Vol. 1-2 and Vol. 1**
REVIEW DIVISION:	**Division of Dermatologic and Dental Drug Products (HFD-540)**
PHARM/TOX REVIEWER:	**Barbara Hill, Ph.D.**
PHARM/TOX SUPERVISOR:	**Paul Brown, Ph.D.**
DIVISION DIRECTOR:	**Jonathan Wilkin, M.D.**
PROJECT MANAGER:	**Millie Wright**

Date of review submission to Division File System (DFS): December 14, 2004

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability – The Cutivate lotion, 0.05% NDA is approvable from a pharmacological/toxicological perspective.

B. Recommendation for nonclinical studies – A study to determine the photocarcinogenic potential of Cutivate lotion, 0.05% is recommended as a Phase 4 commitment.

C. Recommendations on labeling – Recommended wording for the nonclinical portions of the label are provided in the "Suggested labeling" section located at the end of this review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings – Fluticasone propionate elicited the characteristic toxicities associated with a corticosteroid.

B. Pharmacologic activity – Corticosteroid

C. Nonclinical safety issues relevant to clinical use – None at this time

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number:	21-152
Review number:	1
Sequence number/date/type of submission:	000 / 3-12-04 / Original NDA submission BZ / 7-23-04/ Minor amendment
Information to sponsor:	No
Sponsor and/or agent:	GlaxoSmithKline 1500 Littleton Road Parsippany, NJ
Manufacturer for drug substance:	Glaxo Wellcome Inc.

Reviewer name:	Barbara Hill
Division name:	Dermatologic and Dental Drug Products
HFD #:	HFD-540
Review completion date:	12-8-04

Drug:

Trade name: Cutivate lotion, 0.05%

(Note: Sponsor proposed Cutivate 0.05% as the trade name. This was changed to Cutivate lotion, 0.05%, per the chemistry discipline recommendation.)

Generic name: Fluticasone propionate

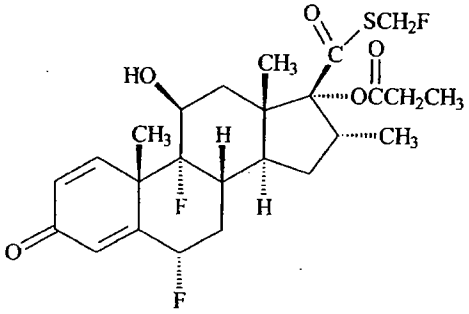
Code name: CCI 18781

Chemical name: Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1- oxopropoxy)-, S-(fluoromethyl) ester, (6-alpha, 11-beta,16-alpha,17-alpha)-

CAS registry number: 80474-14-2

Molecular formula/molecular weight: $C_{25}H_{31}F_3O_5S$ / 500.6

Structure:



Relevant INDs/NDAs/DMFs:

1) IND 28,635 (Cutivate ointment; corticosteroid responsive dermatoses; HFD-540)
2) IND 28,636 (Fluticasone propionate aqueous nasal spray; seasonal or perennial rhinitis and corticosteroid responsive dermatoses; HFD-570)
3) IND 28,765 (Cutivate cream; Corticosteroid-responsive dermatoses; HFD-540)
4) IND 29,039 (Fluticasone propionate inhaler; chronic reversible obstructive disease; HFD-570)
5) IND 40,142 (Fluticasone propionate rotadisk; anti-asthmatic; HFD-570)
6) IND 53,502 (Fluticasone propionate/GR106642X; inhalational maintenance treatment of asthma; HFD-570)
7) IND 54,894 (Cutivate lotion; corticosteroid responsive dermatoses; HFD-540)

1) NDA 19-957 (Cutivate ointment; corticosteroid responsive dermatoses, HFD-540, approved 12-14-90)
2) NDA 19-958 (Cutivate cream; corticosteroid responsive dermatoses, HFD-540, approved 12-18-90)
3) NDA 20-121 (Flonase nasal spray; relief of the symptoms of seasonal or perennial rhinitis, HFD-570, approved 10-19-94)
4) NDA 20-548 (Flovent aerosol; maintenance treatment of bronchial asthma, HFD-570, approved 3-27-96)
5) NDA 20-549 (Flovent/Rotadisk inhalation powder; maintenance treatment of bronchial asthma, HFD-570, approved 11-7-97)
6) NDA 21-077 (Advair diskus {salmeterol/fluticasone propionate}; maintenance treatment of asthma; HFD-570; approved 8-24-00)

Drug class: Corticosteroid, anti-inflammatory

Intended clinical population: Corticosteroid responsive dermatoses

Clinical formulation:

The composition of Cutivate lotion, 0.05%, and the Temovate E vehicle (for comparison purposes) is provided in the following table:

Ingredient	Cutivate lotion (%w/w)	Temovate E vehicle (%w/w)
Fluticasone Propionate,	0.05	--
Cetostearyl Alcohol, NF		
Isopropyl Myristrate, NF		
Dimethicone 360, NF		
(Cetomacrogol 1000)[a]		
Propylene glycol, USP		
Imidurea, NF		
Methylparaben, NF		
Propylparaben, NF		
Citric Acid (Anhydrous), USP		
Sodium Citrate, USP		
Purified Water, USP		

Route of administration: Topical

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Background:

Cutivate Ointment, 0.005%, and Cutivate Cream, 0.05%, were approved in December 1990 for the treatment of corticosteroid responsive dermatoses. The sponsor has developed a line extension Cutivate topical drug product (emulsion formulation) for the treatment of corticosteriod responsive dermatoses. The nonclinical pharmacology/toxicology after oral, dermal or inhalational administration of fluticasone propionate has been established under previous NDAs (listed above). It was determined during the initial review of the nonclinical data available for fluticasone proprionate that no additional nonclinical dermal toxicity studies (except for a photocarcinogenicity study which will be discussed in more detail later) would need to be conducted to support the current formulation. It was determined that the oral and dermal carcinogenicity studies conducted under the Cutivate ointment and Cutivate cream NDAs would be adequate to support the safety of the Cutivate lotion (additional details will be provided below). The vehicle for the Cutivate lotion is similar to the vehicle used in another of the sponsor's marketed products, Temovate E. The Temovate E vehicle has been evaluated in nonclinical and clinical testing to support market approval. The nonclinical evaluation for the Temovate E vehicle included dermal irritation, dermal sensitization, photoirritation and acute toxicity studies.

Glaxo Wellcome originally submitted this NDA on December 13, 1999. It was voluntarily withdrawn six months into the review process on May 25, 2000. The sponsor stated at the time that it was decided that this product line was not in their strategic plan. Glaxo Wellcome and SmithKline Beecham under went a merger subsequent to the withdrawal of the NDA to form GlaxoSmithKline, the current sponsor of this NDA submission. The sponsor states that the merger resulted in renewed interest in the Cutivate lotion drug product

NDA reactivation briefing document when the drug product had been previously referred to as Cutivate lotion). The sponsor believes that the drug product is more properly named Cutivate lotion. The chemistry review team has informed the sponsor that Cutivate lotion is a more appropriate name.

The following two Pharmacology/Toxicology comments were relayed to the sponsor in the 74 day letter (via Fax on May 24, 2004) to address two concerns noted during the filability review.

1) It is recommended that the sponsor update the nonclinical portions of the Cutivate label (i.e., Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy sections under the PRECAUTIONS heading of the label) to current labeling standards. It is recommended that the sponsor use the labeling format for these sections of the label used in the more recently approved fluticasone proprionate drug products such as FLONASE® nasal spray and ADVAIR DISKUS®.

   The division acknowledges receipt of the previously requested estimate of maximum daily human topical dose of Cutivate in mg/kg and mg/m^2. It is recommended that the sponsor include multiples of human exposure levels (based on mg/m^2 comparisons) in the nonclinical portions of the Cutivate label based on the submitted estimate of the maximum daily human topical dose of the Cutivate It is requested that the sponsor submit the calculations used to determine the multiples of human exposure levels to be incorporated into the Cutivate label.

2) It is recommended that the sponsor conduct a study to determine the photoco-carcinogenic potential of Cutivate as a Phase 4 commitment. The division acknowledges that the sponsor is not willing to commit to conducting a photoco-carcinogenicity study in hairless mice. However, alternative study designs for determining the photoco-carcinogenic potential of a topical drug product may be acceptable as noted in the guidance titled "Guidance for Industry – Photosafety testing" published in May, 2003. It would be appropriate to propose use of an alternative study design discussed in the photosafety testing guidance document. It is recommended that the sponsor submit to the NDA their timeline for submitting a protocol to determine the photoco-carcinogenic potential of Cutivate and for conduct of the study to determine the photoco-carcinogenic potential of Cutivate

The Sponsor submitted an amendment to NDA 21-152 on July 23, 2004. This submission addressed the informational requests relayed to the sponsor on May 24, 2004 by the various review disciplines. The Sponsor provided an updated package insert incorporating their version of revised nonclinical portions of the label based on the Division's recommendations. The requested calculations that were used to determine the multiples of human exposure in the updated label were included in the submission.

The Sponsor states in the submission that they do not believe that a photo-carcinogenic study is warranted in this case based on the published FDA guidance titled, "Photosafety Testing," May 2003. The Sponsor provided an updated justification for their position in the submission. The Sponsor has attempted to address issues raised in the "Photosafety Testing" guidance to support their claim. The updated justification provided by the Sponsor in this submission is reviewed under the "Carcinogenicity" section to determine the adequacy to support a waiver for conduct of a study to determine the photoco-carcinogenic potential of Cutivate lotion, 0.05%.

Studies reviewed within this submission:

The list of nonclinical toxicology studies that have been conducted to support the safety of the fluticasone propionate is provided below. These studies were submitted for the approval of Cutivate ointment, 0.005% and/or Cutivate cream, 0.05% (NDA 19-957 and NDA 19-958, respectively). A summary of the results from these studies are provided in this review. The reader is referred to the original NDA reviews for additional detail, if needed.

Repeat Dermal Dose Toxicity Studies

1) 28-day repeat dose skin irritation study in rabbits (Study# NTX/96/002)
2) Five week percutaneous study to assess the local irritancy of an ointment formulation in AHA albino rats (Study# WPT/84/103)
3) Thirty-one day repeat dose dermal toxicity study on abraded skin of rats (Study#WPT/89/010)
4) 35-day repeat dose epicutaneous toxicity study; repeated applications to the abraded skin of RH rats (Study# WPT/89/006)
5) Five week repeat dose dermal toxicity study in rats (Study# UDE/91/006)
6) Maximum repeatable epicutaneous dose studies in RH rats (Study# WPT/88/057)
7) Six month epicutaneous toxicity study in RH rats (Study# WPT/87/126)
8) 26 week dermal toxicity study to dogs (Study# WPT/87/103)
9) 6-month dermal toxicity study in dogs (Study# WPT/87/093)

Repeat Oral and Subcutaneous Dose Toxicity Studies

1) Two week oral toxicity study in RH rats (Study# WPT/84/083)
2) 30-day repeat dose oral toxicity study in rats (Study# WPT/88/041)
3) 26-week repeat dose oral toxicity study in rats (Study# WPT/88/091)
4) A seven day oral dose range finding study in Beagle dog (Study# WPT/86/187)

5) 13-week repeat dose oral toxicity study in dogs (Study# WPT/86/224)
6) 26-week repeat dose oral toxicity study in dogs (Study# WPT/87/213)
7) 90-day repeat dose oral toxicity study in mice (Study# WPT/86/210)
8) 35 to 36 day subcutaneous toxicity study in RH rats (Study# WPT/84/088)
9) Effects of subcutaneous administration to juvenile AHA rats (Study# WPT/88/150)
10) 35-day subcutaneous toxicity study in Beagle dogs (Study# WPT/85/115)

Genotoxicity Studies

1) Ames test and fluctuation test using *S. typhimurium* strains and *E. Coli* (Study# WPT/84/049)
2) Chinese hamster assay (Study# WPT/87/209)
3) Chromosomal aberration assay in human peripheral lymphocytes (Study# WPT/87/087)
4) Mouse micronucleus assay following oral or subcutaneous administration (Study# WPT/85/137)
5) Mouse micronucleus assay following subcutaneous administration (Study# WPT/93/569)

Carcinogenicity Studies:

1) Mouse oral carcinogenicity study (Study# WPT/89/020)
2) Mouse dermal carcinogenicity study (Study# WPT/88/086)
3) Rat inhalation carcinogenicity study (Study# WPT/89/110)

Reproductive Toxicity Studies

1) Fertility and general reproductive performance in rats: Subcutaneous dosing for 60 days prior to mating in males and 14 days prior to mating in female animals (Study# WPT/86/137)
2) Segment II reproductive toxicity study with s.c. administrations during day 6 to day 15 of pregnancy in mice (Study# WPT/85/210)
3) Segment II reproductive toxicity study with s.c. administrations during day 6 to day 15 of pregnancy in rats (Study# WPT/85/190)
4) Segment II reproductive toxicity study with s.c. administrations during day 8 to day 20 of pregnancy in rabbits (Study# WPT/86/043)
5) Segment II reproductive toxicity study with s.c. administrations during day 8 to day 20 of pregnancy in rats (Study# WPT/86/193)
6) Peri/Post natal toxicity study in rats treated subcutaneously from day 17 of pregnancy to the end of lactation (Study# WPT/88/130)

Special Toxicity Studies

1) CCI8781: Primary skin irritation test of fluticasone propionate ointment in rabbits (Study# 090943)

2) CCI8781: Primary skin irritation test of fluticasone propionate cream in rabbits (Study# 090944)
3) Primary skin irritation test of fluticasone propionate solution in rabbits (Study# NTX/95/010)
4) Contact sensitization potential in guinea pigs (Study# WPT/89/001)
5) Phototoxicity test of fluticasone propionate (Study# 090961)
6) Phototoxicity test of fluticasone propionate cream in guinea pigs (Study# 090962)
7) Photocontact sensitivity of Cutivate cream in guinea pigs (Study# NTX/95/003)
8) Eye irritancy study of fluticasone propionate ointment, cream and scalp formulations in rabbits (Study# NTX/96/001; 090945)
9) Cumulative skin irritation study on fluticasone propionate cream for 28 days in NZW rabbits (Study# 090946)
10) Primary skin irritation assay with fluticasone propionate cream in guinea pigs (Study# WPT/86/116; WPT/86/114; WPT/86/113; WPT/86/121)
11) 7-day behavioral toxicity study in rats and dogs (Study# WNP/88/061)

Studies not reviewed within this submission: N/A

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The following information concerning fluticasone propionate pharmacological activity is proposed under the "CLINICAL PHARMACOLOGY" section in the Cutivate lotion label. Information that is highlighted is additional information inserted into the Cutivate lotion label that was not contained in the Cutivate cream/ointment label.

"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 the induction of phospholipase A_2 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 common precursor, arachidonic acid.

Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

Fluticasone propionate is lipophilic and has a strong affinity for the glucocorticoid receptor.

The therapeutic potency of

glucocorticoids is related to the half-life of the glucocorticoid-receptor complex. The half-life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.

Fluticasone propionate has weak affinity for the progesterone receptor, and virtually no affinity for the mineralocorticoid, estrogen, or androgen receptors.

Reviewer's comments: It is unclear if the additional information incorporated into the Cutivate lotion label is necessary or appropriate. The reviewing Clinical Pharmacology and Biopharmaceutics reviewer will determine the adequacy of the additional information.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Refer to brief summary

Drug activity related to proposed indication: Refer to brief summary

2.6.2.3 Secondary pharmacodynamics

Fluticasone propionate was without androgenic, estrogenic, anabolic and anti-gonadotrophic activities. Some progestational activity was demonstrated in rabbits. Anti-estrogenic activity was noted in both rats and mice. Fluticasone propionate possessed anti-androgenic activity in both rats and mice and was anti-anabolic in rats. Fluticasone propionate did not cause sodium retention but did increase sodium and potassium excretion rates in adrenalectomized rats.

2.6.2.4 Safety pharmacology

Fluticasone propionate had no significant effects on the cardiovascular, respiratory or gastrointestinal systems, or on the central and peripheral autonomic nervous systems.

2.6.2.5 Pharmacodynamic drug interactions – N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY – N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Predominantly, single dose studies were conducted with ^{3}H-fluticasone propionate in the mouse, rat and dog in order to characterize the pharmacokinetics, tissue distribution, metabolism and excretion of fluticasone. Systemic exposure to fluticasone

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox-2

2.6.4.2 Methods of Analysis – N/A

2.6.4.3 Absorption

Fluticasone propionate was absorbed after oral administration to rats but was cleared rapidly via first pass metabolism through the liver. Therefore, very little drug was available systemically. The subcutaneous bioavailability of fluticasone in rats was ~90%. Absorption of fluticasone from topical applications to rats as a 0.05% cream or ointment was ~5% from both formulations.

2.6.4.4 Distribution

Radioactivity was widely distributed in the rat after intravenous administration of ^{3}H-fluticasone with the highest levels noted in liver, adrenals, fat and gastrointestinal tract. No prolonged retention of radiolabel was noted in any tissue. No binding to melanin was noted in pigmented rats.

2.6.4.5 Metabolism

The major route of metabolism of fluticasone was hydrolysis of the S-fluoromethyl carbothioate group to yield a carboxylic acid, GR36264. This metabolite was the major metabolite detected in biliary and fecal samples in the rat. Oxidative de-fluorination also occurred in the dog to yield GR100151 (the 6-hydroxy analogue of GR36264).

2.6.4.6 Excretion

Following intravenous administration, the majority of fluticasone was rapidly eliminated from plasma with a half-life of 0.65 and 1.4 hours in rats and dogs, respectively. A small proportion of the dose (<10%) was associated with adipose tissue and eliminated more slowly with a half-life of 4 hours in rats and 10 hours in dogs. Clearance occurred by hepatic metabolism with a hepatic extraction ratio close to unity. Essentially all of the fluticasone metabolites are excreted via the feces and no fluticasone was eliminated intact.

2.6.4.7 Pharmacokinetic drug interactions – N/A

2.6.4.8 Other Pharmacokinetic Studies

The in vitro binding of fluticasone to rat, dog, and human plasma proteins was high (81 – 97%), but the binding to red blood cells was minimal. Some transfer of fluticasone metabolites across the placenta and excretion into milk during lactation was noted in rats following subcutaneous administration of ^{3}H fluticasone.

2.6.4.9 Discussion and Conclusions

Adequate pharmacokinetic studies have been conducted with fluticasone propionate. No additional nonclinical pharmacokinetic studies are recommended for Cutivate Lotion, 0.05%.

2.6.4.10 Tables and figures to include comparative TK summary – N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY – N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Repeat dose toxicology studies have been conducted after topical, subcutaneous, oral and inhalation administration primarily in rats and dogs. The inhalation toxicity studies are not described in this review. Studies ranged in duration from ~1 week to 6 months. The changes observed in these studies were representative of those associated with high doses of glucocorticoids.

Dermal effects noted in repeat dose dermal toxicology studies conducted with fluticasone propionate ointment and cream formulations included slight erythema/edema at the application site. Characteristic steroid related signs of reduced skin thickness were noted in these studies. The effect on skin thickness appeared time dependent and resulted from a reduction in dermal fat and collagen. Healing of abraded skin tended to be prolonged in these studies. The dermal effects were generally time and dose dependent and reversible during the post dose period.

Systemic toxicity noted in repeat dose dermal toxicology studies included decreased body weight gain, increased hemoglobin concentration, decreased lymphocyte count, increase platelet count, increases in serum cholesterol and albumin concentrations, and decreases in the size of the adrenal gland and thymus. The noted treatment related effects were predominantly dose dependent and reversible following dose cessation. The magnitude of these treatment related findings were generally slight at low dermal doses.

Systemic toxicity noted at high dermal doses included body weight loss, adrenal atrophy and thymic involution, increased concentrations of liver enzymes and creatinine in the serum, decreased spleen weight and increased relative weights of the liver and kidney. HPA axis suppression as measured by endogenous glucocorticoid (base and post synacthen challenge) concentrations were noted at high dermal doses. These treatment related effects were dose and time dependent and reversible during recovery periods.

More severe glucocorticoid related changes were noted after high oral doses administered for 6 months or after high subcutaneous doses administered for 1 month. Progressive changes not noted after low doses in repeat dose systemic toxicology studies included decreased lymph node mass, muscle wasting, hepatocellular changes consistent with glycogen depletion, suppression of uterine and ovary development and signs of Cushing's syndrome in dogs. All of these treatment related changes were typically associated with continued exposure to high systemic doses of glucocorticoids.

Genetic toxicology:

Fluticasone propionate was evaluated for genotoxicity in a battery of in vitro and in vivo genetic toxicology studies.

The following information concerning fluticasone propionate genetic toxicology is contained in the Cutivate ointment/cream label.

Fluticasone propionate was not mutagenic in the standard Ames test, *E. coli* fluctuation test, *S. cerevisiae* gene conversion test, or Chinese Hamster ovarian cell assay. It was not clastogenic in mouse micronucleus or cultured human lymphocyte tests.

Reviewer's comment: It is recommended that this section of the label be reworded to current standards for the Cutivate lotion label.

Carcinogenicity:

An oral mouse carcinogenicity study, a dermal mouse carcinogenicity study and an inhalational rat carcinogenicity study have been conducted with fluticasone propionate. The results from the oral and dermal mouse carcinogenicity studies are summarized below.

Oral (gavage) doses of 0 (vehicle), 0 (untreated), 0.1, 0.3 and 1 mg/kg/day fluticasone propionate were administered to mice for 18 months. No treatment related effect on survival was noted in this study. No treatment related tumors were noted in this study.

Dermal doses (40 µl) of 0.05% fluticasone propionate ointment were administered either 1, 3 or 7 days/week for 80 weeks. The group that was dosed 3 days/week was dosed on Monday, Wednesday and Friday. The high dose used in this study was (0.04 ml/day x 0.005 mg/ml ÷ 0.030 kg = 0.0067 mg/kg/day) control groups were dosed with

ointment vehicle (40 µl) 7 days/week or were untreated. No treatment related effect on survival was noted in this study. No treatment related tumors were noted in this study.

The following information concerning fluticasone propionate carcinogenicity is contained in the Cutivate ointment/cream label.

Two 18-month studies were performed in mice to evaluate the carcinogenic potential of fluticasone propionate when given topically (as an 0.05% ointment) and orally. No evidence of carcinogenicity was found in either study.

Reviewer's comment: It is recommended that this section of the label be reworded to current standards for the Cutivate lotion label.

It was recommended that the sponsor conduct a study to determine the photoco-carcinogenic potential of Cutivate lotion as a Phase 4 commitment (relayed to the sponsor in the 74 day letter faxed on May 24, 2004). It was recommended that the sponsor refer to the following guidance document for additional detail (Guidance for Industry – Photosafety testing). It was recommended that the sponsor submit to the NDA their timeline for submitting a protocol to determine the photoco-carcinogenic potential of Cutivate lotion and for conduct of the study to determine the photoco-carcinogenic potential of Cutivate lotion.

The Sponsor submitted an amendment to NDA 21-152 on July 23, 2004. The Sponsor states in the submission that they do not believe that a photo-carcinogenic study is warranted in this case based on the published FDA guidance titled, "Photosafety Testing," May 2003. The Sponsor provided an updated justification for their position in the submission. Review of the newly submitted information is provided below.

The first piece of evidence presented by the sponsor is that Cutivate lotion, 0.05% dissolved in acetonitrile exhibited a maximum wavelength absorption at [redacted] with no appreciable absorption in the [redacted] range. In addition, nonclinicial and clinical photoirritation studies were negative for topical fluticasone propionate ointment or cream formulations. Therefore, Cutivate lotion, 0.05% appears not be photoreactive. The sponsor did state that they understand that demonstrating that Cutivate lotion, 0.05% was not photoreactive would not be adequate to waive the need to determine the photoco-carcinogenic potential of Cutivate lotion, 0.05%.

The sponsor presented data to try to support their view that corticosteroids as a class of drugs do not enhance UV-induced skin carcinogenesis either directly or by non-photoreactive mechanisms and that these compounds, in fact, inhibit tumor formation and progression and exhibit antiphotocarcinogenic effects. The sponsor summarized information contained in several literature articles that described the protective effect of several corticosteroids on UV induced carcinogenesis. Five of the literature references that will be discussed briefly in this review are provided below.

1) Bissett DL, et al. Photoprotective effect of topical anti-inflammatory agents against ultraviolet radiation-induced chronic skin damage in the hairless mouse. *Photodermatol. Photoimmunol. Photomed.* **7:** 153-158, 1990.
2) Kligman LH, Crosby MJ. Topical tretinoin enhances corticosteroid-induced inhibition of tumorigenesis in hairless mice previously exposed to solar simulating radiation. *Cancer Letters* **107:** 217-222, 1996.
3) Kirnbauer R, Kock A, Neuner P, et al. Regulation of epidermal cell interleukin-6 production by UV light and corticosteroids. *J Invest. Dermatol.* **96:** 484-489, 1991.
4) Lowe NJ, et al. Inhibition of ultraviolet-B epidermal ornithine decarboxylase induction and skin carcinogenesis in hairless mice by topical indomethecin and triamcinolone acetonide. *Cancer Research* **42:** 3941-3943, 1982.
5) Budunova IV, Kowalcyk D, Perez P, Yao YJ, Jorcano JL, Slaga TJ. Glucocorticoid receptor functions as a potent suppressor of mouse skin carcinogenesis. *Oncogene* **22:** 3279-3287, 2003.

Female albino hairless mice were irradiated with UVA and UVB radiation for 3 to 5 times weekly for more than 25 weeks in the study described in reference 1. Hydrocortisone, ibuprofen or naproxen, prepared as solutions in a propylene glycol, ethanol and water vehicle, or vehicle alone were applied to the dorsal skin of mice 2 hours prior to each irradiation. The results of this study showed that hydrocortisone caused a reduction in the occurrence of UVB-induced skin wrinkling, tumor formation and histological alterations and UVA-induced skin sagging and histological alterations. Hydrocortisone treatment was also reported to reduce tumor prevalence and significantly delay tumor onset.

The study described in reference 2 investigated the effects of tretinoin and difluorone acetate on photocarcinogenesis. Female albino hairless mice were irradiated 3 times weekly for 10 weeks with 1.5 MED of solar simulated radiation (UVA and UVB). After the initial irradiation period, mice were topically treated with difluorone acetate, tretinoin, emollient vehicle or a sequential combination of difluorone acetate and tretinoin 3 times weekly for 30 weeks. The results of the study showed that topical treatment with difluorone acetate significantly reduce tumor incidence and yield in comparison to UVA and UVB irradiated controls used in the study.

Reviewer's comments: Unfortunately not much information about the UV lamps and filters was included in the literature articles. The lamps used in these studies may have been sunlamps that had UVC present (with inadequate filtering). A drug that absorbs UVC might appear to be protective in these studies versus UVC exposure. In addition, an important question that is not addressed in these studies is whether any "protective" effect (which all anti-inflammatory drugs may possess) could be outweighed by optical effects. The first reference study was conducted with hydrocortisone dissolved in propylene glycol, which does not mimic the composition of the Cutivate lotion vehicle. It is not clear what is the composition of the emollient vehicle used in the second reference study. Results from photoco-carcinogenesis studies conducted in hairless mice

to support the safety of other topical drug products have demonstrated that the optical properties of the vehicle (i.e., enhance the UV exposure to the skin) frequently are the predominant effect for enhancement of photoco-carcinogenesis. It appears that the optical effect may be stronger than any additional immunosuppressive effect based on the results of these studies. Therefore, it would be important to determine the photoco-carcinogenic potential of Cutivate lotion.

The sponsor argues that since corticosteroids down regulate mediators of inflammation, including cytokines, which are involved with tumor promotion, then this supports a protective mechanism for corticosteroids for UV induced carcinogenesis. Epidermal cells produce a variety of cytokines including interleukin (IL)-6, IL-1 and IL-3. UV radiation has been shown to be a potent inducer of cytokine synthesis in epidermal cells. The effects of corticosteroids on IL synthesis in UV irradiated epidermal cells was investigated in an in vitro study described in reference 3. This study demonstrated that normal human epidermal cells irradiated with UVB in vitro were shown to have significantly increased levels of IL-6. Addition of hydrocortisone, prednisolone or dexamethasone immediately after UVB irradiation to the culture media significantly blocked UVB induced IL-6 expression and production by the epidermal cells.

A wide range of tumor promoters, including chemical, physical and UV stimuli, induce cutaneous ornithine decarboxylase. Several literature studies suggest that ornithine decarboxylase induction is an obligatory process in mouse skin carcinogenesis. The study described in reference 4 evaluated the effect of triamcinolone acetonide on induction of epidermal ornithine decarboxylase in the skin of hairless mice. Female albino hairless mice were irradiated with UVB once daily for 20 days. Triamcinonlone acetonide, or indomethacin, prepared in an acetone vehicle, or acetone alone, were topically applied to the dorsal skin of mice immediately after each irradiation. After the initial 20 day treatment period mice were maintained for an additional 49 weeks. The results of this study indicated that triamcinolone acetonide caused an 80% inhibition of epidermal ornithine decarboxylase induction by UVB and markedly reduced the incidence of UVB-induced tumors to 50% of that noted in the acetone vehicle group.

One other interesting article that the sponsor refers to is reference 5. The study contained in this reference studied the mechanism of glucocorticoid inhibition of tumorigenesis. Transgenic mice overexpressing the glucocorticoid receptor were used in this study to show that glucocorticoid receptor overexpression in the epidermis dramatically inhibited skin tumor development after TPA administration. The authors of this study concluded that the results of this study provided in vivo evidence that the glucocorticoid receptor plays a tumor suppressor role in skin carcinogenesis induced by oncogenic ras, possibly through transrepression of NFκB-dependent genes and alteration of proliferation/apoptosis/differentiation of transformed keratinocytes.

The sponsor states that as part of the safety evaluation, many of the clinical studies conducted with topical fluticasone propionate formulations included visual examination of treated skin throughout the treatment period for signs of cutaneous atrophy, straie or pre-atrophogenic changes such as telangiectasia. The sponsor states

that the results for these clinical studies with a treatment period of up to 16 weeks resulted in no significant clinical signs of cutaneous atrophy. In addition, the sponsor conducted a clinical study that evaluated the kinetics and skin thinning induced by fluticasone propionate cream, 0.05% versus vehicle cream following topical application of 0.6 g once daily for 2, 4, 6 or 8 weeks. Skin thickness was measured before and after treatment using pulsed A-scan ultrasound. Telangiectasia and cutaneous atrophy were assessed by visual examination and surface microscopy. Biopsies of treated and untreated skin were taken at the end of each treatment period and evaluated for mean epidermal thickness using an image analysis technique. No treatment related telangiectasia or cutaneous atrophy were noted after the visual examinations and surface microscopy evaluations. A mean decrease in skin thickness of 1-5% was noted after ultrasound evaluation for fluticasone propionate 0.5% cream treated sites compared to vehicle cream treated sites, which was independent of treatment duration. The sponsor states that hydrocortisone cream 1.0% applied twice daily for 6 weeks resulted in a 13% reduction in skin thickness when evaluated by ultrasound measurements. Histological examination of skin biopsy samples for mean epidermal thickness revealed that on average the thickness of skin samples treated with fluticasone propionate cream, 0.05% were 5.6 µm less than those treated with vehicle cream, which was independent of treatment duration. The sponsor concludes that the results of this study demonstrate the low atrophogenic potential of fluticasone propionate cream, 0.05% following topical application for up to 8 weeks. It appears that topical treatment with fluticasone propionate cream, 0.05% did not drastically decrease total skin thickness based on the results of the conducted clinical studies.

Reviewer's comments: The skin thinning assessed in the clinical studies after administration of fluticasone propionate 0.5% cream may not be an appropriate marker for assessing the photoco-carcinogenic potential of Cutivate lotion. The thinning of the skin measured in the referenced clinical studies measured the thickness of collagen, but not of the stratum corneum. The "Photosafety testing" guidance document refers to measurement of thinning of the "protective" layers of the skin (e.g., the stratum corneum). Therefore, measurement of thinning of the skin by measurement of collagen thickness is not an appropriate marker for photoco-carcinogenic potential.

The information submitted by the sponsor to support a waiver for conduct of a study to determine the photoco-carcinogenic potential of Cutivate lotion in not adequate. One possible approach to address this issue may be to implement a class label warning for patients to stay out of the sun during use of the drug product. This class label warning may be useful because subjects may be lead into a false sense of security when exposed to sunlight due to the vasoconstriction properties of topical corticosteroids. The vasoconstriction properties of topical corticosteroids would decrease a local signal of DNA damage (i.e., sunburn). However, it was decided by the review team during the labeling meeting conducted on December 6, 2004, that conduct of a study to determine the photoco-carcinogenic potential of Cutivate lotion would be provide more useful information. In addition, it was determined during the labeling meeting that a sentence should be incorporate into the nonclinical section of the label to address the fact that a

study has not been conducted to determine the photoco-carcinogenic potential of Cutivate lotion.

One possible study design to determine the photoco-carcinogenic potential of Cutivate lotion would be to conduct a 14 day repeat dose study in minipigs (use of one minipig may be acceptable) with untreated, vehicle treated and Cutivate lotion treated sites exposed to UVB/UVA/VIS light [redacted]. DNA dimers (a relatively good measure of UV exposure) could be measured after 1 day and 14 days of treatment to determine if either vehicle or Cutivate lotion treatment increased the exposure to UVB/UVA/VIS light compared to untreated sites. The Division may deem other study designs that could be proposed by the sponsor as acceptable as well.

In summary, a waiver is not granted for the conduct of a study to determine the photoco-carcinogenic potential of Cutivate lotion, 0.05%. It is recommended that the sponsor conduct a study to determine the photoco-carcinogenic potential of Cutivate lotion as a Phase 4 commitment. The sponsor does not need to conduct a traditional photoco-carcinogenicity study in hairless mice. The sponsor can propose an alternative study design for determining the photoco-carcinogenic potential of Cutivate lotion for evaluation by the division. The sponsor did not propose a timeline for conduct of such a study due to the waiver request. The recommended timeline for conduct of the nonclinical phase 4 commitment is provided in the "Recommendations" section of this review.

Reproductive toxicology:

Studies to determine the effects of fluticasone propionate on fertility and general reproductive performance, embryofetal development and peri- and post-natal development were conducted to support the approval of Cutivate ointment/cream.

Fluticasone propionate was tested for its effects on fertility and general reproduction in rats. Subcutaneous doses of 5 – 100 µg/kg/day were administered to male rats from study day 0 – 60 (10 – 100 µg/kg/day on days 1 – 35 and 5 – 50 µg/kg/day on days 36 – 60) and mated with female rats that were subcutaneously dosed with 5 – 50 µg/kg/day for 14 days prior to mating. Decreased body weight gains (males and females) and food consumption, and an increased incidence of alopecia and scab formation at the injection sties (males) were observed at all dose levels. No treatment related effects on implantation, pre-and post-implantation losses, the duration of pregnancy, or parturition in this study. No treatment related visceral abnormalities were noted in the fetuses. A slight decrease in fetal survival was noted in the high dose female group. A dose related reduction in fetal body weight gain and retardation of fetal skeletal development was noted in this study.

In a second rat fertility and general reproduction study, subcutaneous doses of 0, 5, 15 and 50 µg/kg/day fluticasone propionate were administered to males for 63 days prior to mating and female rats prior to mating and until gestation day 7. All females were sacrificed on gestation day 20 for examination of uterine contents. Alopecia and

scab formation was noted at the injection site, decreased body weight gain and body weight and reduced food consumption were noted at all dose levels. No treatment related effects were noted on estrus cycle, pre-coital interval, copulation rate or gestation rate. Spleen, thymus and adrenal weights were decreased at one or all dose levels. Fetal effects included a dose related reduction in body weights, a reduction in the number of live fetuses and increased resorption at the mid and high dose groups. The incidence of vertebral bodies was also reduced in mid and high dose groups. Exencephalia (3 fetuses), rachischisis (1 fetus), cleft lip (1 fetus), cleft palate (1 fetus) and probocis (1 fetus) was noted in ~2.6% of fetuses from litters of high dose dams.

Subcutaneous embryofetal development studies were conducted with fluticasone propionate in mice, rats and rabbits. The teratogenic effects noted in these studies were characteristic of those after glucocorticoid administration. The results of these studies confirmed that fluticasone propionate has the potential to elicit teratogenic effects in laboratory animals.

Subcutaneous doses of 0, 15, 45 and 150 µg/kg/day of fluticasone propionate were administered to pregnant female mice from gestation days 6 – 15. No treatment related mortality was noted in this study. A dose dependent decrease in maternal body weight gain was noted in this study. Cleft palate (the characteristic glucocorticoid induced effect noted in fetal mice) was noted in less that 1% and ~9% of mid and high dose fetuses, respectively.

Subcutaneous doses of 0, 10, 30 and 100 µg/kg/day of fluticasone propionate were administered to pregnant female rats from gestation days 6 – 15. Decreased maternal body weight gain was noted in the low and mid dose animals with a body weight loss noted in the high dose animals. Fetal effects noted in the high dose group included reduced weight, significant retardation of skeletal ossification and umbilical hernia in 2 fetuses of separate litters. The reduced fetal weight may have been secondary to maternal body weight loss. Apparently umbilical hernia is an effect that has been associated with steroid treatment in rats.

In a second rat embryofetal development study, subcutaneous doses of 0, 10, 30 and 100 µg/kg/day of fluticasone propionate were administered to pregnant female rats from gestation days 7 – 17. A dose related decrease in maternal food consumption and body weight gains was noted in this study. Increased lactation time was noted in mid and high dose animals. Five of 24 high dose dams were sacrificed following the death of their offspring. Reductions in the number of live births, corpora lutea and viability rate were noted in the high dose group. Decreased placental and fetal body weights and a retardation of skeletal ossification were noted in mid and high dose animals. An increased incidence of omphalocele and skeletal variations and a cleft palate were noted in high dose fetuses. Omphalocele was noted in one mid dose fetus. Delayed testes descent, ear separation and vaginal opening were noted in high dose fetuses. An impairment of reflexes and an impairment of rearing was noted in high dose fetuses. The maternal and teratogenic NOAEL was identified as 10 µg/kg/day in this study.

Subcutaneous doses of 0, 0.08, 0.57 and 4 µg/kg/day of fluticasone propionate were administered to pregnant female rabbits from gestation days 6 – 18. Reduced food consumption and an increased incidence of fatty liver was noted in high dose does. Reduced fetal body weight was noted in mid and high dose animals. Retarded ossification of the 5th sternebrae, an increased incidence of visceral variants in lung and liver and anomalies including cleft palate were noted in high dose fetuses. The dose levels selected for this study were based on a dose range finding study that evaluated subcutaneous doses up to 10 µg/kg/day fluticasone propionate. The treatment related effects noted in the dose range finding study were generally more severe and included teratogenic effects commonly noted after treatment with a glucocorticoid at doses of 2 – 10 µg/kg/day fluticasone propionate. Rabbits are generally much more sensitive to the teratogenic effects of corticosteroids.

In a second rabbit embryofetal development study, oral doses of 0, 3, 30 and 300 µg/kg/day were administered to pregnant female rabbits from gestation days 8 – 20. No treatment related toxicities were noted in does or fetuses in this study. However, no fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration. The absence of a treatment related effect after oral dosing was probably related to the absence of or minimal fetal exposure due to poor absorption and/or rapid metabolism by the doe after oral administration. The results of this study suggest that subcutaneous administration of fluticasone propionate is the preferred route for embryofetal development studies.

Subcutaneous doses of 0, 15 and 50 µg/kg/day fluticasone propionate were administered to pregnant rats from gestation day 17 through the end of pregnancy for the peri- and post-natal development study. A marked reduction in body weight, caused in part by a reduction in food consumption, was noted during late pregnancy in high dose animals. Body weights were not effected during the lactation period. No treatment related effects on the development of the F_1 offspring were noted in this study. No treatment related effects on the reproductive performance of the F_1 offspring were noted in this study.

In summary, fluticasone propionate had no apparent effect on the mating performance and fertility of rats. No treatment related effect on parturition, lactation and the development of offspring was noted when fluticasone propionate was given to pregnant rats late in their pregnancy and during lactation. The teratogenic effects noted after subcutaneous administration of fluticasone propionate to mice, rats and rabbits generally occurred at maternally toxic doses and were characteristic of those expected in laboratory animals exposed to corticosteriods.

The placental transfer of radioactivity after subcutaneous or oral administration of 100 µg/kg ^{3}H-fluticasone was determined in pregnant rats. The percentage of the dose transferred across the placenta was higher after subcutaneous dosing (~0.025% at 4 hours) than oral dosing (~0.005% at 1 hour). The distribution of radioactivity in fetal tissue was similar to that seen in adult rats.

Fluticasone propionate was noted in the milk of lactating rats after subcutaneous administration of 10 µg/kg ^{3}H-fluticasone propionate. The peak concentrations of radioactivity in milk were noted 2 hours post dose.

The following information concerning fluticasone propionate reproductive toxicology is contained in the Cutivate ointment/cream label. Cutivate ointment/cream is designated as Pregnancy Category C.

In a fertility and general reproductive performance study in rats, fluticasone propionate administered subcutaneously to females at up to 50 mcg/kg per day and to males at up to 100 mcg/kg per day (later reduced to 50 mcg/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.

Corticosteroids 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/day and 150 mcg/kg/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. CUTIVATE Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reviewer's comments: It is recommended that this section of the label be reworded to current standards for the Cutivate lotion label. The rat and rabbit embryofetal development and rat fertility and general reproductive studies are not described in the Cutivate cream/ointment label. The rat placental transfer data for fluticasone propionate are not included in the Cutivate cream/ointment label. It is recommended that the Cutivate lotion label incorporate the results of these studies.

The rat peri- and post-natal development study is not described in the Cutivate cream/ointment label. The rat peri- and post-natal development study should not be incorporated in the Cutivate lotion label because this study may not have been adequately designed or adequately measured post-natal development.

The rat milk transfer data for fluticasone propionate are not included in the Cutivate cream/ointment label. The rat milk transfer data for fluticasone propionate does not need to be incorporated into the Cutivate lotion label because adequate wording was proposed to address this concern. The proposed wording for the "Nursing Mothers" section of the Cutivate lotion label is provided below. Incorporation of the rat milk transfer data for fluticasone propionate would not add any additional useful information to this section of the label.

"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 CUTIVATE EF Emulsion is administered to a nursing woman."

Special toxicology:

A 0.5% fluticasone solution was minimally irritating (very slight erythema) to intact and abraded rabbit skin. No ocular irritation was noted after instillation of 0.1% fluticasone propionate cream to rabbit eyes. Fluticasone cream and ointment formulations did not elicit photoirritation in guinea pig skin. Fluticasone propionate solution was not a sensitizer or photosensitizer in guinea pigs. However, a fluticasone cream formulation may have the potential to elicit a sensitization and/or photosensitization reaction in guinea pigs. However, the cream base used in this study contained excipients, such as a potential sensitizer benzyl alcohol at 2.0%, that are not contained in the marketed cream or new lotion formulations.

A repeat insult patch test study was conducted in humans with Cutivate lotion, 0.05%. The sponsor states that the results from this study indicated no clinically significant irritation and no sensitization potential.

2.6.6.2 Single-dose toxicity

No nonclinical single-dose toxicity studies were included in this submission.

2.6.6.3 Repeat-dose toxicity

No nonclinical repeat-dose toxicity studies were included in this submission.

2.6.6.4 Genetic toxicology

No nonclinical genetic toxicology studies were included in this submission.

2.6.6.5 Carcinogenicity

No nonclinical carcinogenicity studies were included in this submission.

2.6.6.6 Reproductive and developmental toxicology

No nonclinical reproductive and developmental toxicology studies were included in this submission.

2.6.6.7 Local tolerance

No nonclinical local tolerance studies were included in this submission.

2.6.6.8 Special toxicology studies

No nonclinical special toxicology studies were included in this submission.

2.6.6.9 Discussion and Conclusions

Adequate nonclinical toxicology studies have been conducted with fluticasone propionate to support the safety of Cutivate lotion, 0.05%. No additional nonclinical toxicology studies are recommended for Cutivate lotion, 0.05%.

2.6.6.10 Tables and Figures – N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

Refer to summaries provided above.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

NDA 21-152 for Cutivate lotion, 0.05% is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the "Suggested labeling" section are incorporated into the Cutivate lotion label and the sponsor agrees to the Phase 4 commitment described in the "Recommendations" section.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues for NDA 21-152, at this time.

Recommendations:

It is recommended that the suggested labeling changes provided in the next section be incorporated into the Cutivate lotion, 0.05% label.

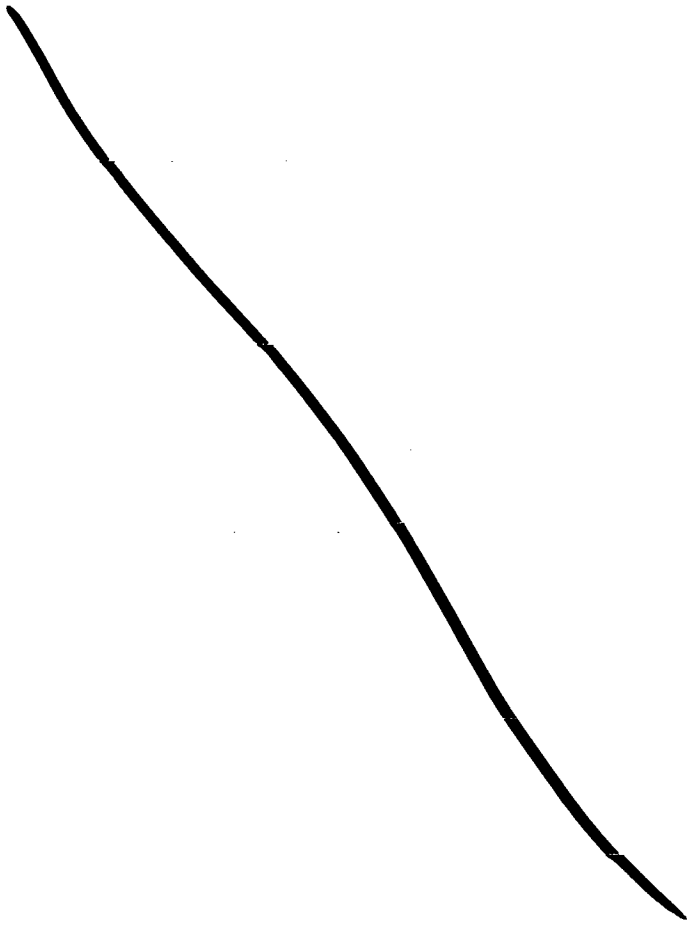
It is recommended that the following nonclinical Phase 4 commitment information be included in an approval letter for Cutivate lotion, if the drug product is approved from the perspective of the other reviewing disciplines.

1. The applicant commits to conducting a study to determine the photocarcinogenic potential of Cutivate (fluticasone propionate) lotion. The applicant

is referred to the guidance document titled "Guidance for Industry – Photosafety testing" published in May, 2003 for assistance in appropriate study design.

Study protocol submission:	By August 15, 2005
Study start date:	By April 15, 2006
Final report submission:	By August 15, 2007

Suggested labeling:



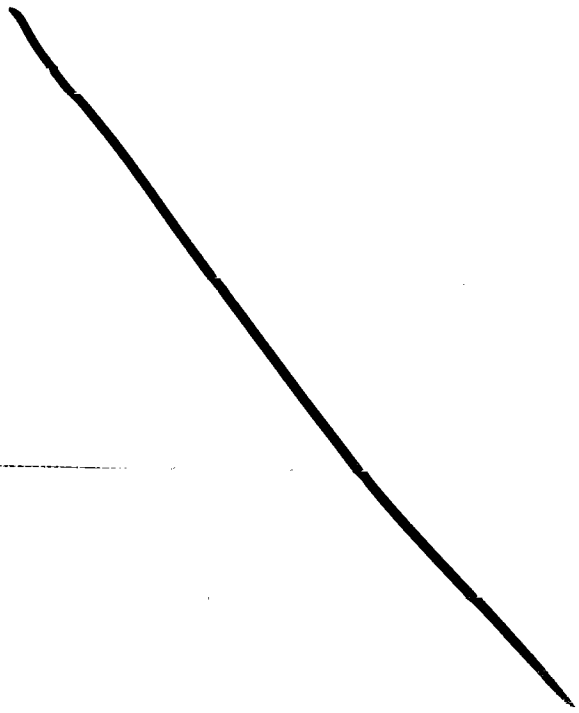
2 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox-3



Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

cc:
HFD-540/DIV DIR/WILKIN
HFD-540/PHARM SUP/BROWN
HFD-540/PHARM/HILL
HFD-540/MO/ALBERT
HFD-540/CHEM/FENSELAU
HFD-540/PM/WRIGHT

APPENDIX/ATTACHMENTS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Barbara Hill
12/14/04 01:56:55 PM
PHARMACOLOGIST

Paul Brown
12/17/04 09:08:54 AM
PHARMACOLOGIST