

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-758

PHARMACOLOGY REVIEW



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: 21-758
SERIAL NUMBER: 000 and BZ
DATE RECEIVED BY CENTER: 4/12/04 and 7/21/04
PRODUCT: cream, 0.1%
INTENDED CLINICAL POPULATION: Corticosteroid responsive dermatoses
SPONSOR: Medicis Pharmaceutical Corp.
DOCUMENTS REVIEWED: Electronic NDA submission
REVIEW DIVISION: Division of Dermatologic and Dental Drug Products (HFD-540)
PHARM/TOX REVIEWER: Barbara Hill, Ph.D.
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PROJECT MANAGER: Melinda Harris

Date of review submission to Division File System (DFS): 12-13-04

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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability – The _____ cream, 0.1% NDA is approvable from a pharmacological/toxicological perspective.
- B. Recommendation for nonclinical studies – A dermal carcinogenicity study conducted with _____ cream and a study to determine the photoco-carcinogenic potential of _____ cream are recommended as Phase 4 commitments.
- 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 – Fluocinonide elicited the characteristic toxicities associated with a corticosteroid.
- B. Pharmacologic activity – Corticosteroid
- C. Nonclinical safety issues relevant to clinical use – None at this time

**Appears This Way
On Original**

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-758
Review number: 1
Sequence number/date/type of submission: 000 / 4-12-04 / Original NDA submission
BZ / 7-21-04/ Minor amendment
Information to sponsor: No
Sponsor and/or agent: Medicis Pharmaceutical Corp.
8125 N. Hayden Road
Scottsdale, AZ 85258

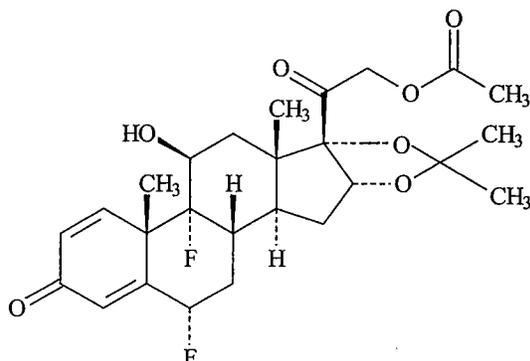
Manufacturer for drug substance: _____

Reviewer name: Barbara Hill
Division name: Dermatologic and Dental Drug Products
HFD #: HFD-540
Review completion date: 12-1-04

Drug:

Trade name: _____ cream, 0.1%
Generic name: Fluocinonide cream, 0.1%
Code name: N/A
Chemical name: Pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-6,9-difluoro-11-hydroxy-16,17-[(1-methylethylidene)bis(oxy)]- (6 α , 11 β , 16 α)-
CAS registry number: 356-12-7
Molecular formula/molecular weight: C₂₆H₃₂F₂O₇ / 494.5
UV absorption: No significant absorption was noted for fluocinonide alone or 0.1% fluocinonide cream over the measured spectrum from _____ 1.

Structure:



Relevant INDs/NDAs/DMFs:

- 1) IND 61,701 (Fluocinonide cream, 0.1%; corticosteroid responsive dermatoses; HFD-540}
- 2) NDA 16-908 (Lidex {Fluocinonide} cream, 0.05%; corticosteroid responsive dermatoses; HFD-540; approved 6-30-71)
- 3) NDA 16-909 (Lidex {Fluocinonide} ointment, 0.05%; corticosteroid responsive dermatoses; HFD-540; approved 9-22-71)
- 4) NDA 17-373 (Lidex {Fluocinonide} gel, 0.05%; corticosteroid responsive dermatoses; HFD-540; approved 5-15-73)
- 5) NDA 18-849 (Lidex {Fluocinonide} solution, 0.05%; corticosteroid responsive dermatoses; HFD-540; approved 4-6-84)

Drug class: Corticosteroid, anti-inflammatory

Intended clinical population: Corticosteroid responsive dermatoses

Clinical formulation:

The composition of the ~~cream~~ cream, 0.1% is provided below.

| Ingredient | % w/w |
|---|-------|
| Fluocinonide micronized, USP | 0.10 |
| Propylene glycol, USP | |
| Dimethyl isosorbide cream | |
| Carbopol 980, NF | |
| Diisopropanolamine cream USP | |
| Citric acid, USP | |
| Glyceryl monostearate, NF | |
| Glyceryl monostearate & PEG stearate cream | |
| Purified water, USP | |

Route of administration: Topical

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

Background:

Fluocinonide is a synthetic corticosteroid for topical dermatological use. It is effective in the treatment of corticosteroid responsive dermatoses primarily because of its anti-inflammatory and antipruritic actions. Fluocinonide is a potent corticosteroid and after topical administration can be absorbed in sufficient amounts to produce systemic effects, including reversible hypothalamic-pituitary-adrenal axis suppression. The sponsor has developed _____ (fluocinonide) cream, 0.1% as a Class I super-high potency topical corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestation of corticosteroid responsive dermatoses. The sponsor has determined that the _____ cream, 0.1% is a Class I corticosteroid based on the results of vasoconstriction clinical studies. The sponsor currently markets Lidex drug products that include fluocinonide 0.05% cream, gel, ointment and topical solution that are all rated as Class II topical corticosteroids and Lidex-E emollient cream rated as a Class III topical corticosteroid.

An End-of-Phase 2 meeting was conducted with the sponsor on April 23, 2003. A pre-NDA meeting was conducted with the sponsor on January 15, 2004. During the pre-NDA meeting it was recommended that the final study reports for three genetic toxicology studies (Bacterial reverse mutation assay, in vitro mammalian chromosome aberration test in human peripheral blood lymphocytes and an in vivo mouse micronucleus assay) conducted with fluocinonide be included with the NDA submission. The final study reports for the three genetic toxicology studies were included in NDA submission.

The sponsor was informed during the pre-NDA meeting that treatment of corticosteroid dermatoses is a chronic indication. Therefore, a nonclinical dermal carcinogenicity study and a study to determine the photoco-carcinogenic potential of 0.1% fluocinonide cream were recommended as phase 4 commitments. It was recommended that the proposed timeline for conduct of both nonclinical studies as Phase 4 commitments be included with an NDA submission for 0.1% fluocinonide cream.

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

1)

- 2) The sponsor does acknowledge the Division's recommendation for two additional nonclinical Phase 4 studies to support _____ cream, 1) a non-clinical dermal carcinogenicity study and 2) a study to determine photoco-carcinogenic potential of the product. However, a formal commitment to conduct the recommended Phase 4 studies with a corresponding timeline was not included in the NDA submission.

It is recommended that the Sponsor submit information to the NDA to clarify the Sponsor's commitment to conduct the two recommended nonclinical Phase 4 studies and provide the corresponding timeline for conduct of each study.

The Sponsor submitted an amendment to NDA 21-758 on July 21, 2004. This submission addressed the informational requests relayed to the sponsor on June 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 adequacy of the revised wording for the nonclinical portions of the label is addressed in the "Suggested labeling" section of this review.

The sponsor stated in the amendment that they intend to conduct 2 additional nonclinical Phase 4 studies to support _____ cream: 1) a dermal carcinogenicity study and 2) a study of the photoco-carcinogenic potential of the product. The sponsor provided a timeline for the conduct of the two Phase 4 nonclinical studies. The proposed timeline is reviewed under the "Carcinogenicity" section of this review.

Studies reviewed within this submission:

The list of nonclinical toxicology studies that have been conducted to support the safety of the fluocinonide is provided below. Studies are identified as either previously reviewed (with corresponding NDA/IND number) or included with the NDA submission. A summary of previously reviewed nonclinical toxicology studies is provided in this review. In addition, the genotoxicity study final study reports are reviewed in this document since they have not been previously submitted to the agency.

Repeat Dermal Dose Toxicity Studies

Note: Several repeat dose systemic and/or dermal toxicology studies were conducted to support the various topical formulations of fluocinonide 0.05%. The overall toxicity profile for fluocinonide was the anticipated toxicities for corticosteroids. It was recommended that a 90 day minipig dermal toxicology study be conducted with the higher strength fluocinonide topical formulation to serve as a bridge to the existing nonclinical toxicology database. The results of the 90 day minipig dermal toxicology study are summarized in this review. The reader is

referred to the previous NDA reviews for a summary of nonclinical toxicology data available for the other topical formulations of fluocinonide.

- 1) A 90-day dermal toxicity study of 0.1% fluocinonide cream in micro-pigs (Submitted to IND 61,701, Serial# 020)

Genotoxicity Studies

Note: The final study reports for the genotoxicity studies listed below were included in this NDA submission and are reviewed in this document.

- 1) Bacterial reverse mutation assay
- 2) In vitro mammalian chromosome aberration test
- 3) In vivo mammalian erythrocyte micronucleus test

Reproductive Toxicity Studies

- 1) Rabbit topical/oral teratology study (Submitted to NDA 16-908)

Special Toxicity Studies

- 1) Acute eye irritation study of 0.1% fluocinonide cream in albino rabbits (Submitted to IND 61,701, Serial# 020)
- 2) Skin sensitization study of 0.1% fluocinonide cream in albino guinea pigs (Magnusson and Kligman Maximization technique) (Submitted to IND 61,701, Serial# 020)

Studies not reviewed within this submission: N/A

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The following information concerning fluocinonide pharmacological activity is contained in the proposed label under the "CLINICAL PHARMACOLOGY" section.

"Like other topical corticosteroids, fluocinonide 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 A2 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 A2."

Reviewer's comment: The information contained in this section of the label appears to be relatively standard information that describes the mechanism of action for corticosteroids.

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 – N/A

2.6.2.4 Safety pharmacology

No safety pharmacology studies have been conducted with fluocinonide. No safety pharmacology studies are recommended for fluocinonide at this time.

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

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and occlusive dressings will increase the percent of percutaneous absorption. Following absorption, topical corticosteroids are metabolized in the liver and excreted primarily by the kidneys. Small amounts of both parent compound and metabolites are excreted in the bile.

The following information concerning fluocinonide pharmacological activity is contained in the proposed **■■■■** label under the “CLINICAL PHARMACOLOGY; Pharmacokinetics” section.

“The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Vasoconstrictor studies performed with **■■■■**TM Cream indicate that it is in the super-high range of potency as compared with other topical corticosteroids.”

Reviewer's comments: The information contained in this section of the label appears to be relatively standard information that describes the pharmacokinetics for corticosteroids. The reviewing Clinical Pharmacology and Biopharmaceutics reviewer will determine the adequacy of this information.

2.6.4.2 Methods of Analysis – N/A**2.6.4.3 Absorption – Refer to brief summary****2.6.4.4 Distribution – Refer to brief summary****2.6.4.5 Metabolism – Refer to brief summary****2.6.4.6 Excretion – Refer to brief summary****2.6.4.7 Pharmacokinetic drug interactions – N/A****2.6.4.8 Other Pharmacokinetic Studies – N/A****2.6.4.9 Discussion and Conclusions**

No additional nonclinical pharmacokinetic studies are recommended for **—** cream, 0.1%.

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:

The sponsor conducted a 90 day repeat dose dermal toxicology study in micropigs with the clinical formulation of the 0.1% fluocinonide cream. Topical doses of 0 (0.9 g/kg/day vehicle cream), 150 (0.15 g/kg/day 0.1% fluocinonide cream), 450 (0.45 g/kg/day 0.1% fluocinonide cream) and 900 (0.9 g/kg/day 0.1% fluocinonide cream) mg/kg/day fluocinonide were administered in this study. This study was conducted by varying the amount of a set concentration of fluocinonide cream (0.1%) applied to a designated treatment area. In effect this would cause an increase in the thickness of the layer applied to the treatment area. It can not be presumed that diffusion through a thick layer of fluocinonide cream would be greater than through a thin layer of fluocinonide cream. A better design for this study would have been to apply a set amount of fluocinonide cream at the treatment site and vary the concentration of fluocinonide in the cream formulation up to the maximum feasible concentration for the high dose group. However, the results of this study demonstrated characteristic toxic effects noted after systemic corticosteroid administration. Decreased body weights were noted in the high dose group. Atrophy of the skin was noted in all treatment groups. Effects on the adrenal gland that included decreased weight and mild to minimal cortical atrophy (all zones) of the adrenal

cortex were noted in mid and high dose animals. A sign of systemic immunosuppression, bronchopneumonia, was noted in low, mid and high dose animals. Neither a dermal or systemic NOAEL could be established in this 90 day repeat dose dermal toxicology study conducted with 0.1% fluocinonide cream in micropigs.

The general toxicity profile for corticosteroids is well established. The results of the 90 day micropig repeat dose dermal toxicology study confirmed the general toxicity profile for fluocinonide. No additional repeat dose toxicology studies are recommended for _____ cream, 0.1%.

Genetic toxicology:

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

Fluocinonide was tested in the Ames test at concentrations of 15, 50, 150, 500, 1500 and 5000 µg/plate. Fluocinonide was negative in the Ames test, under the conditions of this study.

Fluocinonide was tested in the in vitro mammalian chromosome aberration test using human peripheral blood lymphocytes. The doses chosen for the chromosome aberration assay ranged from 62.5 – 2500 µg/plate. Fluocinonide was negative for the induction of structural and numerical chromosomal aberrations in the in vitro mammalian chromosome aberration test using human peripheral lymphocytes, under the conditions of this study.

Fluocinonide was tested in the in vivo mouse micronucleus assay. Single intraperitoneal doses of 0, 500, 1000 and 2000 mg/kg fluocinonide were administered to ICR mice (5/sex/dose). A positive control (cyclophosphamide) was incorporate into this study. Bone marrow cells were collected from all treatment groups at 24 hours after dose administration and also at 48 hours after treatment in the vehicle and high dose groups. Reductions in the ratio of polychromatic erythrocytes to total erythrocytes were observed in the test article treated groups relative to the vehicle control group. These reductions demonstrate bioavailability of the test article to the bone marrow target. A significant increase in micronucleated polychromatic erythrocytes was observed in low dose females and mid and high dose animals 24 hours post dose and high dose animals 48 hours post dose. In addition, there was evidence of a dose related increase in the number of micronucleated polychromatic erythrocytes observed in male and female mice over the three test article dose levels 24 hours post dose. The results of this study indicate that single intraperitoneal doses of fluocinonide at doses up to 2000 mg/kg induced a significant increase in the number of micronucleated polychromatic erythrocytes in male and female ICR mice. Therefore, it was concluded that fluocinonide was positive in the in vivo mouse micronucleus assay, under the conditions of this study.

In summary, fluocinonide was negative in the Ames test and the in vitro mammalian chromosome aberration test. Fluocinonide was positive in the in vivo mouse micronucleus assay. Other potent corticosteroids have demonstrated positive signals in genetic toxicology studies. It is recommended that the results from these genotoxicity studies be incorporated into the _____ cream, 0.1% label. It is anticipated that the extent of systemic exposure to

fluocinonide after topical application of [redacted] cream, 0.1% will be much less than was achieved in the in vivo mouse micronucleus assay.

The sponsor has conducted a full battery of genetic toxicology studies for fluocinonide according to ICH guidelines. No additional genetic toxicology studies are recommended for [redacted] cream, 0.1%, at this time.

Carcinogenicity:

A nonclinical dermal carcinogenicity study has not been conducted with any topical fluocinonide formulation. In addition, a study to determine the photoco-carcinogenic potential of [redacted] cream has not been conducted by the sponsor. It was recommended that the sponsor conduct both these studies as phase 4 commitments. The sponsor has included the following timeline for conduct of both studies. The information provided below was copied directly from the NDA supplement submitted on July 21, 2004.

In accord with the Division's recommendations, upon approval of the product, Medicis intends to conduct 2 additional nonclinical Phase 4 studies to support [redacted] Cream. These will be (1) a dermal carcinogenicity study and (2) a study of the photocarcinogenic potential of the product. Medicis has outlined a timeline for the conduct of these studies in 5 steps, as follows (the 2 studies will be conducted concurrently):

Step 1: Development of Dosing Formulations

In this step, dosing formulations for the nonclinical studies, using an appropriate vehicle for the drug substance, will be developed. Estimated duration: 6 months.

Step 2: Development and Validation of Analytical Methodology

In this step, assays will be developed and validated for the detection of fluocinonide in the nonclinical study dosing formulations, and in rat plasma and mouse serum. Assays will be developed and validated for the detection of corticosterone and cortisone (cortisol) in rat plasma and mouse serum. Stability testing of fluocinonide in the nonclinical study dosing formulations will be conducted. Estimated duration: 6 months.

Step 3: 90-day Dose Range-Finding Studies

In this step, following the validation of analytical methods, two 90-day studies will be performed, one in rat and one in mouse, to determine the appropriate dosing for the 2-year studies. Endpoints will include clinical signs, body weight, food consumption, clinical chemistry, plasma (serum) glucocorticoids and ACTH, organ weights, and gross and microscopic histopathology. Estimated duration: 10 months.

Step 4: FDA Review and Approval of Nonclinical Study Designs

In this step, Medicis will prepare and submit a proposal to the Division for the design of the nonclinical studies, based on the results of the dose-ranging studies. Estimated duration for preparation of the submission and FDA review: 6 months.

Step 5: Conduct of 2-year Nonclinical Studies

Estimated duration, from initiation of the studies to submission of the final report: 42 months.

The expected timelines are summarized in the table below:

| Step | Description | Duration (mos) |
|--------------|--|----------------|
| 1 | Development of Dosing Formulations | 6 |
| 2 | Development and Validation of Analytical Methodology | 6 |
| 3 | 90-day Dose Range-Finding Studies | 10 |
| 4 | FDA Review and Approval of Nonclinical Study Designs | 6 |
| 5 | Conduct of 2-year Nonclinical Studies | 42 |
| Total | | 70 |

It appears that the sponsor is proposing conduct of a traditional photoco-carcinogenicity study in hairless mice to determine the photoco-carcinogenic potential of **████** cream. The proposed timeline for conduct of the two Phase 4 nonclinical studies appears to be reasonable, except for the estimated time for conduct of the photoco-carcinogenicity study. An estimate of 42 months to conduct and submit a final study report for a 2 year dermal carcinogenicity study appears reasonable. However, an estimate of 42 months for conduct of a traditional photoco-carcinogenicity study is too long. The treatment duration for a traditional photoco-carcinogenicity study is 52 weeks (40 weeks of treatment with a 12 week follow up period). Therefore, the treatment duration for a traditional photoco-carcinogenicity study is 1 year less than a 2 year dermal carcinogenicity study. The estimated time for submission of a final study report from a traditional photoco-carcinogenicity study should be 12 months less (i.e., 30 months) than for the 2 year dermal carcinogenicity study (i.e., 42 months). The recommended timeline for conduct of the two nonclinical phase 4 commitments is provided in the "Recommendations" section of this review.

Reviewer's comment: Conduct of a dermal carcinogenicity study and a study to determine the photoco-carcinogenic potential of **████** cream, 0.1% appears prudent in light of the positive genotoxicity signal noted for fluocinonide in the in vivo mouse micronucleus assay.

Reproductive toxicology:

Apparently, only one teratology study that has been conducted with fluocinonide. During the pre-NDA meeting, the sponsor stated that there exists a rabbit teratology study of fluocinonide administered topically and orally, which was previously submitted in NDA 16-908. The sponsor agreed to submit a detailed summary of the rabbit teratology study with the NDA submission. The sponsor stated during the pre-NDA meeting that no other teratology investigations have been performed with fluocinonide.

During the pre-NDA meeting, the sponsor proposed to use the same wording contained in the Lidex label for the reproductive and developmental toxicology portion of the cream, 0.1% label. The wording contained in the Lidex label is the standard information for the nonclinical reproductive toxicology associated with topical corticosteroids. It was determined that this would be acceptable. No additional reproductive and developmental toxicology studies were recommended for 0.1% fluocinonide cream since the sponsor agreed to incorporate appropriate wording into a label for the cream.

The results from the summary rabbit teratology study report provided in the NDA submission is provided below. According to the summary information provided in the NDA submission, this study was conducted in the 1950s/1960s.

Fifteen pregnant female rabbits (Fauve de Bourgogne strain) were used in this study. The dose groups used in this study are provided in the following table.

| Dose (mg/kg) | Route of Administration | # of animals | Sacrifice | |
|--------------|-------------------------|--------------|-----------|-------|
| | | | GD 22 | PN 10 |
| 0 | Topical | 4 | 2 | 2 |
| 0.005 | | 2 | | 2 |
| 0.02 | | 2 | 2 | |
| 0.05 | | 2 | | 2 |
| 0.20 | | 2 | 2 | |
| 0 | Oral | 1 | 1 | |
| 0.005 | | 1 | 1 | |
| 0.05 | | 1 | 1 | |

GN – gestational day; PN – postnatal day 10

Pregnant female rabbits were exposed to either topical or oral daily doses of fluocinonide from one week prior to mating through gestational day 15. It was not specified in the summary information what topical formulation of fluocinonide was used in this study. The fetuses were examined for malformations on either gestation day 22 or postnatal day 10 as outlined in the table. The summary information states that there were no treatment related effects on the number of fetuses, fetal weight, placental weight or malformations in the oral or topically treated groups. An increase in the number of resorptions was noted in the topically treated groups but not in the orally treated groups.

The data provided in the summary report for this study is of limited value. No information concerning the fluocinonide topical formulation was provided in the summary report. The number of animals used in this study is not adequate to allow accurate conclusions to be drawn from the summary data provided. In addition, it is not clear if an adequate high dose was selected for either the oral or topical portion of this study. Therefore, no adequate nonclinical dermal or systemic teratology studies have been conducted with fluocinonide. However, animal studies with various corticosteroids has shown that in sufficient doses these agents can induce specific teratogenic effects (e.g. cleft palate) in susceptible species (mice, rats

and rabbits)^{1,2,3}. In addition, literature reports demonstrate that corticosteroids can inhibit fetal growth in animals and humans^{4,5}.

Reviewer's comments: The information that is contained in the summarized rabbit teratology study is very limited at best. The division informed the sponsor during the pre-NDA meeting that their proposal to incorporate the standard corticosteroid reproductive toxicology information in the _____ cream, 0.1% label would be adequate. No additional reproductive and developmental toxicology studies are recommended for _____ cream, 0.1%, at this time. It is recommended that the results from this rabbit teratology study not be included in the Lidex cream, 0.1% label, since it is not an adequate study according to current standards.

Special toxicology:

The 0.1% fluocinonide cream was a mild ocular irritant in rabbits and did not elicit a sensitization response in the Magnusson and Kligman guinea pig maximization test.

The sponsor submitted to IND 61,701 an UVB/UVA/VIS spectrum from _____ for fluocinonide alone and 0.1% fluocinonide cream. The fluocinonide alone spectrum was run with 20 µg/ml concentration in acetonitrile. A peak max was noted at ~240 nm with no absorption past 270 nm. The 0.1% fluocinonide cream was dissolved in acetonitrile and the spectrum was run at a concentration of 20 µg/ml. A peak max was noted at ~240 nm with a very small shoulder of absorbance that continued over in the 280 – 300 nm range. The small shoulder of absorbance noted for the 0.1% fluocinonide is related to the excipients in the cream formulation. I considered this a very minimal level of absorbance. The Lidex (fluocinonide) 0.05% cream has been on the market for over 30 years with no signal of photoirritation. The different excipients used in the new 0.1% fluocinonide cream formulation do not appear to be of concern for a photoirritation reaction. Therefore, the need for a nonclinical photoirritation study for 0.1% fluocinonide cream was waived.

No additional special toxicology studies are recommended for _____ cream, 0.1%, at this time.

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.

¹ Walker B. Induction of cleft palate in rats with antiinflammatory drugs. *Teratology* 4: 39-42, 1971.

² Pinsky L and DiGeorge AM. Cleft palate in the mouse: a teratogenic index of glucocorticoid potency. *Science* 147: 402-403, 1965

³ Fainstat T. Cortisone induced cleft palate in rabbits. *Endocrinology* 55: 502-508, 1954.

⁴ Reinisch JR et al. Prenatal exposure to prednisone in humans and animals retard intrauterine growth. *Science* 202: 436-438, 1978.

⁵ Scorr JR. Fetal growth retardation associated with maternal administration of immunosuppressive drugs. *Am J Obstet Gynecol* 128: 668-676, 1977.

Results

Study validity:

A test article was considered to be positive if it produced at least a 2-fold increase in the spontaneous reversion rate and demonstrated a dose response curve.

Solvent control mean reversion frequencies fell within established ranges. Positive control results were appropriate in this study. The dose range selected for the definitive study was appropriate according to ICH guidelines.

Study outcome:

The test article produced a negative response in the presence and absence of S-9 activation. All of the tester strains treated with the test article exhibited a mean reversion frequency that was similar to the corresponding solvent control.

Genetic toxicology study #2

Study title *In vitro* mammalian chromosome aberration test

Key findings: Fluocinonide was negative in the human lymphocyte chromosome aberration cell assay, with and without S9 activation, under the conditions of this assay.

| | |
|-----------------------------------|------------------------------|
| Study no.: | AA73XX.341. _____ |
| Volume #, and page #: | Electronic NDA submission |
| Conducting laboratory: | _____ |
| Date of study initiation: | 2003 |
| GLP compliance: | Yes |
| QA reports: | Yes |
| Drug, lot #, and % purity: | Fluocinonide, Lot# 131043 |
| Vehicle: | DMSO |

Methods

Strains/species/cell line: Human peripheral blood lymphocytes

Doses used in definitive study:

The chromosomal aberration assay was performed using duplicate suspensions with a treatment period of 4 hours \pm S9 (S9 derived from Aroclor 1254 induced rat liver homogenate) and 20 hours $-$ S9. Cells were harvested 20 hrs after the initiation of treatment. Concentrations of 62.5, 125, 250, 500, 1000, 2000, 2250 and 2500 μ g/ml fluocinonide were tested in the chromosomal aberration study. Concentrations of 250, 500, and 1000 μ g/ml fluocinonide were

selected for analysis of chromosome aberrations. The 2000, 2250 and 2500 µg/ml fluocinonide concentrations were not analyzed due to excessive toxicity.

Basis of dose selection:

In the preliminary toxicity test, concentrations of 0, 0.25, 0.75, 2.5, 7.5, 25, 75, 250, 750 and 2500 µg/ml fluocinonide were tested in cells (incubated at 37 °C) for 4 hours ± S9 and for 20 hours –S9. Cells were harvested 20 hours after initiation of treatment. Toxicity as based upon a reduction in mitotic index relative to the solvent control. Substantial toxicity (i.e., at least 50% reduction in mitotic index relative to solvent control) was noted at 2500 µg/ml fluocinonide in all 3 exposure groups. Concentrations selected for the chromosomal aberration assay were 62.5, 125, 250, 500, 1000, 2000, 2250 and 2500 µg/ml fluocinonide based on the results of the preliminary toxicity test.

Negative controls: DMSO

Positive controls: Mitomycin C (-S9): 0.6 µg/ml for 4 hour exposure and 0.3 µg/ml for 20 hour exposure.
Cyclophosphamide (+S9): 20 µg/ml for 4 hour exposure

Incubation and sampling times:

Cell cultures were incubated with test article for 4 hour ±S9 or 20 hour exposure –S9 at 37 °C and harvested 20 hours after treatment initiation. Slides were prepared from the harvested cultures and stained with 5% Giemsa solution for the analysis of mitotic index and chromosomal aberrations.

Results

Study validity:

A test article was considered to be positive for inducing chromosomal aberrations if a significant increase in the number of cells with chromosomal aberrations was observed at one or more concentrations.

Solvent control mean reversion frequencies fell within established ranges. Positive control results were appropriate for this assay. The dose range selected for the definitive assay was appropriate according to ICH guidelines.

Study outcome:

Fluocinonide was negative for the induction of structural and numerical chromosome aberrations in the in vitro mammalian chromosome aberration test, using human peripheral lymphocytes, in nonactivated and S9-activated test systems.

Genetic toxicology study #3**Study title** *In vivo* mammalian erythrocyte micronucleus test**Key findings:** Fluocinonide was positive in the *in vivo* mouse micronucleus assay, under the conditions of this experiment.

Study no.: AA73XX.123. ~~_____~~
Volume #, and page #: Electronic NDA submission
Conducting laboratory: ~~_____~~
Date of study initiation: 2003
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: Fluocinonide, Lot# 131043 and 135249
Vehicle: Corn oil

MethodsStrains/species/cell line: ICR mice; 6-8 weeks; 19.9-35.9 g; 5/sex/dose/timepointDoses used in definitive study: 0, 500, 1000 or 2000 mg/kg fluocinonide, ipBasis of dose selection: Single doses of 0, 1, 10, 50, 100, 500, 1000 and 2000 mg/kg fluocinonide, ip, were evaluated in a dose range finding toxicity study (5/sex/dose). Piloerection was noted in males treated with 100, 500 and 1000 mg/kg and males and females treated with 2000 mg/kg. Lethargy was noted in males treated with 2000 mg/kg. No mortality was noted in the dose range finding toxicity study. The high dose was set at 2000 mg/kg for the definitive micronucleus study.Negative controls: Corn oilPositive controls: Cyclophosphamide (50 mg/kg), ip (in water)Incubation and sampling times: Single ip doses of fluocinonide or cyclophosphamide were administered to mice. Bone marrow for analysis of nucleated cells was obtained from treated mice 24 hours (5/sex/dose; all treatment groups) and 48 hours (5/sex/dose; vehicle control and high dose groups only) after dose administration.

Stained bone marrow slides were scored for micronucleus and the PCE (polychromatic erythrocytes) to NCE (normal chromatic erythrocytes) cell ratio. The micronucleus frequency (expressed as percent micronucleated cells) was determined by analyzing the number of micronucleated PCEs from at least 2000 PCEs per animal. The PCE:NCE ratio was determined

by scoring the number of PCEs and NCEs observed while scoring at least 500 erythrocytes per animal.

Results

Study validity:

A test article was considered to be positive if there was a statistically significant increase in micronucleated PCEs for at least one dose level, and a statistically significant dose-related response.

Solvent control mutant frequencies fell within established ranges. Positive control results were appropriate. Dose range selected for the definitive study was appropriate according to ICH guidelines.

Study outcome:

No mortality was noted in the definitive study. The only clinical sign noted was piloerection in mid and high dose males.

The summary information for the bone marrow micronucleus assay is provided in the following table (copied from the electronic NDA submission).

**Appears This Way
On Original**

Table 8.3.3.1 Summary of Bone Marrow Micronucleus Analysis Following a Single Dose of Fluocinonide Acetonide in ICR Mice

| Treatment (20 mL/kg) | Sex | Time (hr) | # of Mice | PCE/Total Erythrocytes (Mean ± SD) | Change from Control (%) | Micronucleated Polychromatic Erythrocytes | |
|----------------------|-----|-----------|-----------|------------------------------------|-------------------------|---|------------------------|
| | | | | | | Number per 1000 PCEs (Mean ± SD) | Number per PCEs Scored |
| Vehicle (corn oil) | M | 24 | 5 | 0.534 ± 0.03 | --- | 0.6 ± 0.42 | 6/10000 |
| | F | 24 | 5 | 0.463 ± 0.06 | --- | 0.6 ± 0.22 | 6/10000 |
| FA 500 mg/kg | M | 24 | 5 | 0.447 ± 0.03 | -16 | 1.3 ± 0.91 | 13/10000 |
| | F | 24 | 5 | 0.471 ± 0.01 | + 2 | 1.6 ± 0.42 | 16/10000* |
| FA 1000 mg/kg | M | 24 | 5 | 0.454 ± 0.02 | -15 | 3.5 ± 1.17 | 35/10000* |
| | F | 24 | 5 | 0.402 ± 0.04 | -13 | 4.6 ± 1.29 | 46/10000* |
| FA 2000 mg/kg | M | 24 | 5 | 0.396 ± 0.06 | -26 | 4.7 ± 1.44 | 47/10000* |
| | F | 24 | 5 | 0.387 ± 0.03 | -16 | 5.0 ± 1.06 | 50/10000* |
| CP 50 mg/kg | M | 24 | 5 | 0.314 ± 0.04 | -41 | 21.0 ± 4.60 | 210/10000* |
| | F | 24 | 5 | 0.322 ± 0.01 | -30 | 19.7 ± 1.48 | 197/10000* |
| Vehicle (corn oil) | M | 48 | 5 | 0.527 ± 0.09 | --- | 0.2 ± 0.27 | 2/10000 |
| | F | 48 | 5 | 0.520 ± 0.02 | --- | 0.5 ± 0.00 | 5/10000 |
| FA 2000 mg/kg | M | 48 | 5 | 0.383 ± 0.04 | -27 | 12.4 ± 8.76 | 124/10000* |
| | F | 48 | 5 | 0.367 ± 0.05 | -29 | 9.0 ± 2.62 | 90/10000* |

FA indicates fluocinonide acetonide; CP, cyclophosphamide.

* Statistically significant, $p \leq 0.05$ compared to vehicle (Kastenbaum-Bowman tables).

Reductions of 13% to 29% in the ratio of polychromatic erythrocytes to total erythrocytes were observed in the fluocinonide treated groups compared to vehicle controls. These reductions demonstrate bioavailability of the test article to the bone marrow target. A significant increase in micronucleated polychromatic erythrocytes was noted in low dose females 24 hours after treatment, in mid and high dose animals 24 hours after treatment and in high dose animals 48 hours after treatment compared to control animals ($p \leq 0.05$, Kastenbaum-Bowman tables). In addition, there was evidence of a dose related increase in the number of micronucleated polychromatic erythrocytes observed in male and female mice over the tested dose range 24 hours post-dose.

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

Fluocinonide was positive in the in vivo mouse micronucleus assay. A nonclinical dermal carcinogenicity study has not been conducted with any topical fluocinonide formulation. In addition, a study to determine the photoco-carcinogenic potential of [redacted] cream has not been conducted by the sponsor. It was recommended that the sponsor conduct both these studies as phase 4 commitments. The sponsor has agreed to conduct a dermal carcinogenicity study with [redacted] cream and a study to determine the photoco-carcinogenic potential of [redacted] cream as Phase 4 commitments. Conduct of a dermal carcinogenicity study with [redacted] cream and a study to determine the photoco-carcinogenic potential of [redacted] cream appear prudent in light of the positive genotoxicity signal noted for fluocinonide in the in vivo mouse micronucleus assay.

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:

Based on the nonclinical data available for fluocinonide, NDA 21-718 for [redacted] cream, 0.1% is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the next section are incorporated into the [redacted] cream, 0.1% label.

The sponsor has agreed to conduct a dermal carcinogenicity study with [redacted] cream and a study to determine the photoco-carcinogenic potential of [redacted] cream as Phase 4 commitments. Conduct of a dermal carcinogenicity study with [redacted] cream and a study to determine the photoco-carcinogenic potential of [redacted] cream appear prudent in light of the positive genotoxicity signal noted for fluocinonide in the in vivo mouse micronucleus assay. The recommended timeline for conduct of these nonclinical studies is provided in the "Recommendations" section below.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues for NDA 21-758, at this time.

Recommendations:

It is recommended that the suggested labeling changes provided in the next section be incorporated into the _____ cream, 0.1% label.

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

1. The applicant commits to conducting a dermal carcinogenicity study with _____ (fluocinonide) cream.

| | |
|---|----------------------|
| Development of dosing formulations: | By August 15, 2005 |
| Development and validation of analytical methodology: | By February 15, 2006 |
| 90-day dose range-finding study: | By December 15, 2006 |
| Study protocol submission: | By June 15, 2007 |
| Study start date: | By February 15, 2008 |
| Final report submission: | By August 15, 2011 |

2. The applicant commits to conducting a study to determine the photoco-carcinogenic potential _____ (fluocinonide) cream.

| | |
|----------------------------------|----------------------|
| 90-day dose range-finding study: | By December 15, 2006 |
| Study protocol submission: | By June 15, 2007 |
| Study start date: | By February 15, 2008 |
| Final report submission: | By August 15, 2010 |

Suggested labeling:

1 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Pharm/Tox-

1

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/VAUGHAN
- HFD-540/CHEM/PAPPAS
- HFD-540/PM/HARRIS

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
12/13/04 10:59:19 AM
PHARMACOLOGIST

Paul Brown
12/14/04 10:12:51 AM
PHARMACOLOGIST