

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-844

PHARMACOLOGY REVIEW(S)



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: 21-844
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: December 21, 2005
PRODUCT: Desonate (desonide) gel, 0.05%
INTENDED CLINICAL POPULATION: Corticosteroid responsive dermatoses
SPONSOR: Skin Medica (Sponsor representative – Dow
Pharmaceuticals Sciences)
DOCUMENTS REVIEWED: Electronic cCTD NDA submission
REVIEW DIVISION: Division of Dermatology and Dental Products (HFD-540)
PHARM/TOX REVIEWER: Barbara Hill, Ph.D.
PHARM/TOX SUPERVISOR: Paul Brown, Ph.D.
DIVISION DIRECTOR: Susan Walker, M.D.
PROJECT MANAGER: Shalini Jain

Date of review submission to Division File System (DFS): 7-13-06

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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability – The Desonate gel, 0.05% NDA is approvable from a pharmacological/toxicological perspective.
- B. Recommendation for nonclinical studies – A dermal carcinogenicity study conducted with Desonate gel and a study to determine the photoco-carcinogenic potential of Desonate gel 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 – Desonide 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: 21-844
Review number: 1
Sequence number/date/type of submission: 000 / 12-21-05 / Original NDA submission
Information to sponsor: No
Sponsor and/or agent: Skin Medica
5909 Sea Lion Place, Suite H
Carlsbad, CA 92008

Sponsor representative: Dow Pharmaceuticals Sciences
1330A Redwood Way
Petaluma, CA 94954

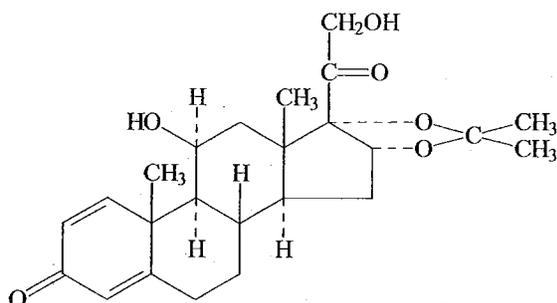
Manufacturer for drug substance: _____

Reviewer name: Barbara Hill
Division name: Dermatologic and Dental Drug Products
HFD #: HFD-540
Review completion date: 6-12-06

Drug:

Trade name: Desonate gel, 0.05%
Generic name: Desonide gel, 0.05%
Code name: N/A
Chemical name: 11 β , 16 α , 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic
16, 17-acetal
CAS registry number: 638-94-8
Molecular formula/molecular weight: C₂₄H₃₂O₆ / 416.5
UV absorption: No significant absorption was noted for desonide
alone or any of the excipients in desonide gel over
the measured spectrum from 225 – 700 nm.

Structure:



Relevant INDs/NDAs/DMFs:

Desonide NDAs:

- 1) NDA 17-010 (Tridesilon {Desonide} cream, 0.05%; Corticosteroid responsive dermatoses; HFD-540; approved 1/4/72; Clay Park Labs)
- 2) NDA 17-426 (Tridesilon {Desonide} ointment, 0.05%; Corticosteroid responsive dermatoses; HFD-540; approved 11/1/74; Clay Park Labs)
- 3) NDA 19-048 (Desowen {Desonide} cream, 0.05%; Corticosteroid responsive dermatoses; HFD-540; approved 12/14/84; Galderma Labs LP)

Generic Desonide ANDAs:

- 1) ANDA 71-425 (Desowen {Desonide} ointment, 0.05%; Corticosteroid responsive dermatoses; HFD-600; approved 5/15/88; Galderma Labs LP)
- 2) ANDA 72-354 (Desowen {Desonide} lotion, 0.05%; Corticosteroid responsive dermatoses; HFD-600; approved 1/24/92; Galderma Labs LP)
- 3) ANDA 73-548 (Desonide cream, 0.05%; Corticosteroid responsive dermatoses; HFD-600; approved 6/30/92; Taro Pharms)
- 4) ANDA 74-027 (Desonide cream, 0.05%; Corticosteroid responsive dermatoses; HFD-600; approved 9/28/92; Copley Pharm)
- 5) ANDA 74-254 (Desonide ointment, 0.05%; Corticosteroid responsive dermatoses; HFD-600; approved 8/3/94; Taro Pharms)
- 6) ANDA 75-751 (Desonide ointment, 0.05%; Corticosteroid responsive dermatoses; HFD-600; approved 3/12/01; Alanta)

IND:

- 1) IND 67,548 (Desonide gel, atopic dermatitis, HFD-540)

Drug class: Corticosteroid, anti-inflammatory

Intended clinical population: Mild to moderate atopic dermatitis in adult and pediatric patients (≥ 3 months)

Clinical formulation:

The composition of the Desonate gel, 0.05% is provided below.

Component	%w/w	
	Nonclinical	Clinical
Desonide	0.05	0.05
Glycerin, USP	—	—
Propylene glycol, USP	—	—
Methylparaben, USP	—	—
Propylparaben, USP	—	—
Edetate disodium, dihydrate, USP	—	—
Carbopol 981 ^a , NF	—	—
Sodium hydroxide	—	—
Purified water	—	—

a – The sponsor included information in the original IND submission that indicated that Carbopol 981 that provided adequate information to assure that the level of benzene contained in Carbopol 981 is basically benzene free according to Agency criteria. The level of Carbopol 981 was —% in the desonide gel used for nonclinical studies and —% in Clinical supplies and in the to-be-marketed Desonate gel. The sponsor states that the concentration of Carbopol 981 was — of the finished product. This small difference (—%) in Carbopol 981 levels does not invalidate any nonclinical studies conducted to support the safety of Desonate gel.

Route of administration: Topical

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

Background:

Desonide is a synthetic, non-halogenated, corticosteroid. Various topical dosage forms of desonide, 0.05% (e.g., DesOwen and Tridesilon) are currently being marketed for the corticosteroid responsive dermatosis indication. The current application provides information for a gel dosage form of desonide. The sponsor has submitted a 505(b)(2) application for desonide gel, 0.05%. In the cover letter for Serial #001 (submitted on January 30, 2006), the sponsor provided clarification for the reference listed drug (RLD) for this application. The sponsor states that the RLD is DesOwen cream, 0.05% from NDA 19-048. Apparently the sponsor used Desowen lotion, 0.05% for clinical studies for comparison to their desonide gel. The sponsor states that the Desowen lotion formulation was approved under ANDA 72-354 and the RLD for that ANDA application is DesOwen cream, 0.05% from NDA 19-048. Therefore, if

the sponsor is able to generate an adequate clinical bridge, then the sponsor can use the nonclinical labeling information contained in the DesOwen cream label to support their desonide gel formulation.

A pre-IND meeting was conducted with the sponsor on April 2, 2002. An End of Phase 2 meeting was conducted with the sponsor on November 20, 2003. A pre-NDA meeting (which was downgraded to a guidance meeting) was conducted with the sponsor on February 10, 2005. During the pre-NDA meeting (which had been downgraded to a guidance meeting), the Division informed the sponsor that their single Phase 3 study would not be adequate to support approval of the desonide gel formulation. The sponsor had conducted a 3 arm Phase 3 clinical study that compared the efficacy of desonide gel, 0.05% to the desonide vehicle and DesOwen lotion. Summary information included in the pre-NDA briefing document indicated that desonide gel was superior to the desonide vehicle but did not meet the non-inferior criteria comparison to DesOwen lotion. The Division informed the sponsor that the single 3 arm Phase 3 clinical study would be adequate to form a safety bridge to DesOwen lotion, but would not be adequate to form an efficacy bridge to DesOwen lotion. Therefore, the sponsor will be able to use the nonclinical toxicology data contained in the DesOwen cream label for the desonide gel label. The Division recommended conduct of a second Phase 3 clinical study comparing the efficacy of desonide gel versus desonide vehicle to provide adequate data to demonstrate the efficacy of desonide gel. The sponsor has conducted the recommended second Phase 3 clinical study and included the results in the NDA submission. This NDA submission is an electronic submission in CTD format.

It was requested that the sponsor provide a comprehensive timeline for conduct of the nonclinical studies to evaluate the dermal carcinogenic and photoco-carcinogenic potential of desonide gel, 0.05%, as postmarketing commitments in the 45 day letter. The 45-day letter was faxed to the sponsor on February 28, 2006. The sponsor provided a response to the requested information in Serial #002 (submitted on March 20, 2006). The adequacy of the response will be addressed under the carcinogenicity subsection contained in Section 2.6.6.1 "Overall toxicology summary" of this review.

Studies reviewed within this submission:

An overview of the nonclinical toxicology study information available for desonide in the literature was provided in this submission and will be discussed in the appropriate nonclinical sections of this document. The sponsor has conducted five nonclinical toxicology studies that were included in the original IND submission. These studies are listed below and summarized in the appropriate nonclinical sections of this document. The reader is referred to the review of the original IND submission for IND 67,548 for additional details, if needed.

- 1) Primary dermal irritation study in rabbits (0215-U2.R-04-02)
- 2) Primary eye irritation study in rabbits (0215-U2.R-05-02)
- 3) Genotoxicity study – Bacterial reverse mutation assay (0215-U2.R-01-02)
- 4) Genotoxicity study – In vitro mammalian cell gene mutation test (L5178Y/TK⁺ mouse lymphoma assay) (0215-U2.R-02-02)
- 5) Genotoxicity study – Mammalian erythrocyte micronucleus test (0215-U2.R-03-02)

Studies not reviewed within this submission: N/A

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

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

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 desonide. No safety pharmacology studies are recommended for desonide, 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

Nonclinical percutaneous absorption studies have been conducted with desonide and triamcinolone acetonide formulated in an emollient cream at a 0.01% concentration. Basically these nonclinical studies compared the extent of absorption from topical administration of 0.01%

desonide cream versus 0.01% triamcinolone acetonide cream in rabbits. The results of these studies suggest that desonide had a greater percutaneous absorption rate compared to triamcinolone acetonide when formulated at the same concentration in the same cream base under various skin conditions (intact, abraded and occluded).

In general, once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

The following information concerning desonide pharmacokinetics activity is contained in the proposed Desonate gel label under the "CLINICAL PHARMACOLOGY; Pharmacokinetics" section.

"The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the _____ and the integrity of the epidermal barrier. _____

Reviewer's comments: The information contained in this section of the label appears to be older standard information that describes the pharmacokinetics for corticosteroids. The 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 desonide gel, at this time.

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 provided a summary of literature acute toxicology studies that have been conducted with desonide. These studies were described in the following literature reference, which was included in the submission.

Philips BM, Sanen FJ, Leeling JL, Hartnagel RE, Sancilio LF, Lorenzetti OJ and Kraus PJ. The physical, animal and human pharmacologic and toxicologic properties of desonide, a new, topically active, antiinflammatory steroid. *Toxicology and Applied Pharmacology*, **20**: 522-537, 1971.

The acute systemic toxicology of desonide has been evaluated in rats after subcutaneous administration. The subcutaneous LD₅₀ in rats was 93 mg/kg. The acute oral toxicology of the desonide cream formulation was evaluated in rats and dogs. Rats were orally administered 0.2% desonide cream (33.3 g cream/kg). No treatment related clinical effects or macroscopic observations were noted in this study. Dogs were orally administered 0.2% desonide cream (10 g cream/kg). No deaths or treatment related macroscopic observations were noted in this study.

A 0.05% cream formulation of desonide (16 g cream/kg) was applied to various skin sites (intact unoccluded, abraded unoccluded, intact occluded, abraded occluded) on 4 groups of rats for 24 hours. No treatment related clinical signs, dermal irritation or deaths were noted in this study. The dermal LD₅₀ for desonide cream 0.05% was >16 g cream/kg in rats.

A 0.2% cream formulation of desonide (16 g cream/kg) was applied to various skin sites (intact unoccluded, abraded unoccluded, intact occluded, abraded occluded) on 4 groups of rabbits for 24 hours. Treatment related dermal reactions varied from very slight to moderate erythema and from no edema to slight edema. No treatment related mortality, clinical signs, effects on hematologic or urologic parameters were noted in this study. The dermal LD₅₀ for desonide cream 0.2% was >16 g cream/kg in rabbits.

The sponsor provided a summary of three literature repeat dose toxicology studies that have been conducted with desonide. The first two studies were described in the first literature

reference provided below. The third study was described in the second literature reference provided below. Both literature references were included in the submission.

- 1) Product Monograph: Tridesilon cream 0.05% (Dome) *Rx Bulletin*, 3 (2): 27-30, 1972.
- 2) Mascitelli-Coriandoli E and Fraia A. Prednacinolone, a new anti-inflammatory steroid. Note 2: Biochemical and pharmacological properties. *Arzneimittel Forschung Drug research*, 20 (1): 111-115, 1970.

A 2 week dermal repeat dose toxicity study was conducted in rabbits with a desonide cream formulation. Rabbits were topically treated with 2 g cream/kg of 0.05%, 0.1% or 0.2% desonide cream. Topical applications were applied daily onto the shaved or abraded back skin of rabbits for two consecutive weeks. The dermal reactions noted in this study were believed to be due to the abrasion technique. Treatment related systemic effects included one death and the monograph states that changes in different organs at the end of treatment indicate that the cutaneous application of the final formulation produced systemic effects. The conclusion derived in the monograph from this study was that it is possible to predict a minimum risk of systemic toxicity with the use of compounds containing desonide.

The subchronic dermal toxicity of desonide was investigated in rabbits, which received daily dermal doses of 0.2, 0.6 or 2 g cream/kg of a desonide cream 0.05% formulation for 13 weeks. One high dose female rabbit died in this study. No treatment related effects on clinical signs or food consumption was noted in this study. No treatment related effects on bodyweight was noted in female animals, but a treatment related decrease in bodyweight was noted in mid and high dose males. No treatment related macroscopic observations were noted in this study. A treatment related increase in liver weight and decrease in adrenal, gonad and spleen weights were noted in this study. No treatment related microscopic observations were noted in this study. The conclusion derived in the monograph from this study is that these findings suggest that the risk of toxicity following chronic dermal application of this material is quite low.

A 2 week systemic repeat dose toxicology study was performed in male Wistar rats. Rats were administered an oral or intraperitoneal dose of 3 mg/kg/day of desonide for 2 weeks. Toxicity parameters that were evaluated in this study included body weight, glucose and BUN levels, liver weight and glycogen content of the liver. Desonide induced several characteristic glucocorticoid toxicity effects including increase bodyweight, increased liver weight and glycogen content, and increased blood glucose and BUN. It appeared that greater toxicity was apparent after oral administration compared to intraperitoneal administration.

Desonide appears to generate a characteristic toxicity profile noted after administration of corticosteroids. The sponsor had proposed in the pre-IND briefing document to conduct a

It was determined that the conduct of this study would not be necessary. It was determined it is unlikely that conduct of this study would provide new information on the toxicity of desonide. Therefore, the sponsor was informed that the

_____ is not necessary if the clinical studies provide a sufficient bridge to the listed drug product.

It appears that the sponsor will be developing desonide gel primarily for a pediatric population. No nonclinical repeat dose dermal toxicology studies have been conducted with any topical formulation of desonide in juvenile animals. However, the effects of corticosteroids in pediatric patients have been well established for systemic and topical corticosteroids. Therefore, it was determined that it is not necessary for the sponsor to conduct nonclinical repeat dose dermal toxicology studies for desonide gel 0.05% in juvenile animals.

In conclusion, no additional general toxicology studies are recommended for desonide gel at this time.

Genetic toxicology:

Desonide was evaluated for genotoxicity in a battery of in vitro and in vivo genetic toxicology studies. Desonide was negative in an in vitro bacterial mutagenesis assay (Ames test) and an in vivo mouse micronucleus assay. Desonide was positive without S9 activation and was equivocal with S9 activation in an in vitro mammalian cell mutagenesis assay (L5178Y/TK⁺ mouse lymphoma assay). It is recommended that the genotoxicity information for desonide be incorporated into the desonide gel label. The recommended wording for this section of the label is provided in the "Recommendations" section of this review.

The sponsor has conducted a full battery of genetic toxicology studies for desonide according to ICH guidelines. No additional genetic toxicology studies are recommended for desonide gel.

Carcinogenicity:

No nonclinical dermal carcinogenicity or photoco-carcinogenicity studies have been conducted with any topical formulation of desonide. The division has determined that treatment of atopic dermatitis is a chronic indication. It is recommended that drug products used in chronic recurring diseases be evaluated for their carcinogenic potential. Therefore, a nonclinical dermal carcinogenicity study and a study to determine the photoco-carcinogenic potential of desonide gel, 0.05% were recommended as phase 4 commitments.

The sponsor submitted a proposal for conduct of a dermal carcinogenicity study in Tg.AC mice with Desonide gel to IND 67,548 in Serial #015 (dated 4-20-04). It was determined that the proposal put forth by the sponsor was acceptable. The following comments were relayed to the Sponsor via Fax concerning the proposed dermal carcinogenicity study.

- 1) The Division has determined that the Sponsor's proposal to conduct a dermal carcinogenicity study with desonide gel using the Tg.AC transgenic mouse model appears acceptable.

- 2) The Division acknowledges the Sponsor's intent to request a review of a protocol for a 28-day range-finding study in the FVB/N mouse to support dose selection for a dermal carcinogenicity study in Tg.AC mice with desonide gel. The Division is receptive to reviewing a protocol for a 28-day range-finding study in the FVB/N mouse to support dose selection for a dermal carcinogenicity study in Tg.AC mice with desonide gel.
- 3) The Division acknowledges the Sponsor's intent to perform a feasibility study to confirm that the TPA positive control elicits an appropriate positive response in the desonide gel vehicle in Tg.AC mice. It is recommended that the feasibility study be conducted prior to the proposed 28-day range-finding study in FVB/N mice. If the TPA positive control does not elicit an appropriate positive response in the desonide gel vehicle in Tg.AC mice, then use of the Tg.AC mouse model for the dermal carcinogenicity study with desonide gel would not be appropriate.
- 4) Please note that the use of a transgenic animal carcinogenicity model in the evaluation of a drug is usually considered appropriate as the second assay of two when the first assay is a traditional 2-year carcinogenicity assay (see ICH S1B). If the Tg.AC assay with desonide gel results in a positive signal, additional testing, possibly including a 2-year carcinogenicity assay, may be recommended.

The sponsor initially proposed to _____

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The Sponsor decided not to _____ The sponsor proposed during the pre-NDA meeting to conduct a 13-week photosafety study in rats to determine the photoco-carcinogenic potential of Desonide gel, 0.05%, as a phase 4 commitment. The revised proposal appeared to be acceptable. The sponsor was informed that the adequacy of the proposed study will be determined after review of the study protocol. It was requested during the pre-NDA meeting that the sponsor include a timeline for the dermal carcinogenicity study and the study to determine the photoco-carcinogenic potential of desonide gel in the NDA submission. The requested timeline was not included in the original NDA submission. The timeline was requested again in the 74-day letter sent to the sponsor on February 28, 2006. The sponsor submitted the requested timeline to the NDA in SN 002 on March 20, 2006. The submitted timeline is provided below.

Dow Pharmaceuticals Sciences, Inc. commits to the following Phase 4 timelines.

Dermal Carcinogenic Transgenic Study

Q1 2007	4-week dose range finding study report (plus TPA feasibility study)
Q2 2007	Study protocol submission
Q4 2007	Study start date
Q2 2009	Final report submission

Photoco-Carcinogenic (13-week photosafety study in mice)

Q1 2007	Pilot study report (single dose SKH1-hr mice studies for PK, irritancy and UVR response)
Q2 2007	Study protocol submission
Q4 2007	Study start date
Q3 2008	Final report submission

The overall timeline proposed by the sponsor for the dermal carcinogenicity study and photoco-carcinogenicity study appear reasonable. However, it is preferable to have actual dates in the timeline for tracking in the Post-marketing study database. Therefore, dates have been inserted into the timeline and the recommended timeline for conduct of the two nonclinical phase 4 commitments is provided in the "Recommendations" section of this review.

The recommended timeline was based on the assumption that the approval date for desonide gel is October 21, 2006 (rounded up to November 1, 2006 for easier calculations). The date for submission of the 28-day dose range finding study is 3 months after the approval date for both studies (February 1, 2007). The date for submission of the study protocol is 3 months after initiation of the 28-day dose range finding study for both studies (May 2, 2007). The date for starting both studies is 6 months after submission of the study protocol (November 1, 2007). The date for submitting the final study reports for the dermal carcinogenicity study and photoco-carcinogenicity study is 18 months and 9 months, respectively, after the study start date (May 1, 2009 and August 1, 2008, respectively).

Reproductive toxicology:

Summary information for two literature dermal embryofetal development studies that were conducted with a desonide cream formulation was provided in the literature reference provided below, which was included in this submission.

Product Monograph: Tridesilon cream 0.05% (Dome) *Rx Bulletin*, 3 (2): 27-30, 1972.

Two dermal embryofetal studies were conducted with a Tridesilon cream 0.05% in rats and rabbits. Doses of 0.2, 0.6 and 2.0 g cream/kg/day of a desonide cream 0.05% formulation or 2 g/kg of the cream base were administered topically to pregnant rats (gestational days 6 – 15) and rabbits (gestational days 6 – 18). An increased incidence of several fetal abnormalities were noted in mid and high dose rats (cleft palate, cleft sternum, missing lower jaw, left rear-club-foot with fused bones, forked ribs, short thickened leg bones). An increased incidence of several fetal abnormalities were noted in high dose rabbits (asymmetry of sternocostals, no parietal, holes in sections of parietal, parietal poorly developed, skull poorly developed). These abnormalities have been previously reported to occur following systemic administration of corticosteroids. Stillborn fetuses (4) were noted in the high dose rat group. Significant increases in resorption sites were observed in both species. Four high dose pregnant rats died during the dosing period. Maternal body weight loss was noted at all dose levels in rats and rabbits. Tridesilon cream 0.05% was teratogenic in rats at topical doses of 0.6 and 2.0 g cream/kg/day and in rabbits at a dose of 2.0 g cream/kg/day. It appears that both of these studies were conducted with high enough doses to elicit maternal toxicity.

No fertility or peri- and post-natal developmental studies have been conducted with desonide.

The following information is included in the Desowen cream/ointment/lotion 0.05% label for the reproductive and developmental toxicity potential of desonide. Desowen cream/ointment/lotion 0.05% is designated as Pregnancy Category C.

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of DesOwen cream, ointment and lotion.

Corticosteroids are generally 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. Animal reproduction studies have not been conducted with DesOwen cream, ointment or lotion. It is also not known whether DesOwen cream, ointment or lotion can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DesOwen cream, ointment and lotion should be given to a pregnant woman only if clearly needed.

Dermal embryofetal development studies have been conducted in rats and rabbits with desonide cream 0.05%. It appears that the characteristic spectrum of teratogenic effects expected after adequate systemic exposure to a corticosteroid was displayed in these two studies. The information from these two studies was not incorporated into the DesOwen cream label. It appears that the two dermal embryofetal development studies were conducted at maternally toxic doses of desonide cream, 0.05%. It is recommended that general information about these two studies be incorporated into the Desonate gel label to indicate that teratogenicity is possible after topical administration of desonide. The recommended wording for this section of the label is provided in the "Recommendations" section of this review. It is important to note that the same wording was recently recommended for the ~~_____~~ (desonide) foam label (NDA 21-978) to provide consistency for topical desonide products.

No fertility or peri- and post-natal developmental studies have been conducted with desonide. It was determined during the pre-IND evaluation of the desonide gel 0.05% briefing document that additional reproductive toxicity studies would probably not be required for an NDA since the label of a corticosteroid would at least contain the information that such products have been previously shown to be teratogenic even after dermal application. Therefore, no additional nonclinical reproductive and developmental toxicology studies are recommended for desonide gel.

Special toxicology:

Desonide gel 0.05% was not a dermal or ocular irritant in rabbits under the conditions of both studies.

The sponsor was informed during the pre-IND meeting that since all of the ingredients have been used previously in approved products a sensitization study in guinea pigs is not considered necessary. Therefore, the need for a nonclinical sensitization study was waived for desonide gel.

The sponsor provided UV absorption spectra (225 – 700 nm) for desonide and each individual component of the desonide gel in the original IND submission. No absorption was noted for either desonide or any individual component of desonide gel in the UVA/UVB/Vis range of 290 – 700 nm. Therefore, the need for a nonclinical photoirritation study was waived for desonide gel, 0.05%. No additional special toxicology studies are recommended for desonide gel.

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

An ICH battery of genotoxicity studies have been conducted with desonide. It is recommended that the results from these studies be incorporated into the Desonate gel label. A nonclinical dermal carcinogenicity study has not been conducted with any topical desonide formulation. In addition, a study to determine the photoco-carcinogenic potential of Desonate gel 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 Desonate gel and a study to determine the photoco-carcinogenic potential of Desonate gel as Phase 4 commitments.

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 desonide, NDA 21-844 for Desonate gel, 0.05% is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the next section are incorporated into the Desonate gel, 0.05% label.

The sponsor has agreed to conduct a dermal carcinogenicity study with Desonate gel and a study to determine the photoco-carcinogenic potential of Desonate gel as Phase 4 commitments. 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 21-844, at this time.

Recommendations:

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

It is recommended that the following nonclinical Post-marketing commitment information be included in an approval letter for Desonate gel, if the drug product is approved from the perspective of the other reviewing disciplines.

1. The applicant commits to conducting a dermal carcinogenicity study in Tg.AC mice with Desonate (desonide) gel.

28-day dose range-finding study:

Study protocol submission:

Study start date:

Final report submission:

2. The applicant commits to conducting a study to determine the photo-carcinogenic potential of Desonate (desonide) gel (13-week photosafety study in mice).

Study protocol submission:

Study start date:

Final report submission:

Suggested labeling:

The nonclinical portions of the Desonate gel, 0.05% label are provided below. It is recommended that the highlighted wording be inserted into and the ~~strikeout~~ wording be deleted from the "Carcinogenicity, Mutagenesis, and Impairment of Fertility" and "Pregnancy" sections of the Desonate gel, 0.05% label.

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this page is the manifestation of the electronic signature.**

/s/

Barbara Hill

7/13/2006 11:37:21 AM

PHARMACOLOGIST

Nonclinical post-marketing commitments to be relayed to sponsor

Paul Brown

7/13/2006 12:38:25 PM

PHARMACOLOGIST

Memorandum

To: NDA 21-844
From: Barbara Hill, Ph.D., Pharmacology/Toxicology Reviewer
Through: Paul Brown, Ph.D., Pharmacology/Toxicology Supervisor
Re:

Submission date: 8-30-06
Serial No.: 000
Submission type: 4P, Nonclinical post-marketing commitments
Drug: Desonate (desonide) gel, 0.05%
Drug class: Corticosteroid, anti-inflammatory
Indication: Mild to moderate atopic dermatitis in adult and pediatric patients (≥ 3 months)
Sponsor: Skin Medica, Carlsbad, CA
Sponsor's agent: Dow Pharmaceuticals Sciences, Petaluma, CA

Review date: September 7, 2006

Clinical formulation:

The composition of the Desonate gel, 0.05% is provided below.

Component	%w/w
Desonide ()	
Glycerin, USP	
Propylene glycol, USP	
Methylparaben, USP	
Propylparaben, USP	
Edetate disodium, dihydrate, USP	
Carbopol 981, NF	
Sodium hydroxide	
Purified water	

Introduction:

Desonide is a synthetic, non-halogenated, corticosteroid. Various topical dosage forms of desonide, 0.05% (e.g., DesOwen and Tridesilon) are currently being marketed for the corticosteroid responsive dermatosis indication. The current application provides information for a gel dosage form of desonide. The sponsor has submitted a 505(b)(2) application for desonide gel, 0.05%. In the original NDA submission the sponsor proposed a timeline for the two recommended nonclinical post-marketing commitments (a dermal carcinogenicity study and a study to determine the photoco-carcinogenic potential of desonide gel) that were determined to be acceptable. The sponsor has proposed a new timeline for conduct of the two recommended nonclinical post-marketing commitments. The adequacy of the new timeline is addressed in the next section of this document.

The original proposed timeline for the nonclinical post-marketing commitments is provided below.

Dermal Carcinogenic Transgenic Study

- Q1 2007 4-week dose range finding study report (plus TPA feasibility study)
- Q2 2007 Study protocol submission
- _____ Study start date
- _____ Final report submission

Photoco-Carcinogenic (13-week photosafety study in mice)

- Q1 2007 Pilot study report (single dose SKH1-hr mice studies for PK, irritancy and UVR response)
- Q2 2007 Study protocol submission
- _____ Study start date
- _____ Final report submission

The original timeline proposed by the sponsor for the dermal carcinogenicity study and photoco-carcinogenicity study appeared reasonable. However, actual dates are needed for the timeline for tracking in the Post-marketing study database. Therefore, the following timeline was relayed to the sponsor (via fax on 8-23-06) that incorporated dates into the timeline for the nonclinical post-marketing commitments.

1. The applicant commits to conducting a dermal carcinogenicity study in Tg.AC mice with Desonate (desonide) gel.

28-day dose range-finding study: _____
Study protocol submission: _____
Study start date: _____
Final report submission: _____

2. The applicant commits to conducting a study to determine the photoco-carcinogenic potential of Desonate (desonide) gel (13-week photosafety study in mice).

_____ _____
Study protocol submission: _____
Study start date: _____
Final report submission: _____

Reviewer's comments: The 90-day dose-range finding study referenced in the second nonclinical post-marketing commitment was a typographical error and should have been a 21-day dose-range finding study as proposed by the sponsor. The sponsor was informed of this typographical error on August 28, 2006 via email.

Revised timeline for nonclinical post-marketing commitments:

The sponsor submitted the following revised timeline for the nonclinical post-marketing commitments.

Dermal Carcinogenic Transgenic Study

- Q2 2007 4-week Dose Range Finding Study Report (plus TPA feasibility study)
- Q4 2007 Study Protocol Submission
- Q3 2008 Study Start Date
- Q2 2010 Final Report Submission

Photoco-Carcinogenic (13-week photosafety study in mice)

- Q2 2007 Pilot Study Report (single dose SKH1-hr mice studies for PK, irritancy and UVR response)
- Q3 2007 Study Protocol Submission
- Q1 2008 Study Start Date
- Q1 2009 Final Report Submission

Reviewer's comments: The sponsor's revised timeline has increased the amount of time for the various steps in each nonclinical post-marketing commitment. The increase in time for each step of the dermal transgenic carcinogenicity study timeline is provided below.

- 3 months increase for approval to dose range finding study report submission
- 3 months increase for study protocol submission
- 3 months increase for study start date
- 3 months increase for final report submission

The total increase in time for the revised timeline for the dermal transgenic carcinogenicity study is 12 months. The revised timeline for the dermal transgenic carcinogenicity study appears acceptable.

The increase in time for each step of the 13-week photosafety study in mice timeline is provided below.

- 3 months increase for approval to dose range finding study report submission
- 0 months increase for study protocol submission
- 0 months increase for study start date
- 3 months increase for final report submission

The total increase in time for the revised timeline for the 13-week photosafety study in mice is 6 months. The revised timeline for the 13-week photosafety study in mice appears acceptable.

The revised timelines proposed by the sponsor for the dermal transgenic carcinogenicity study and 13-week photosafety study in mice appear reasonable. However, it is preferable to have actual dates in the timelines for tracking in the Post-marketing study database. Therefore, dates have been inserted into the timeline and the recommended timeline for conduct of the two nonclinical post-marketing commitments is provided in the "Recommendations" section.

The recommended timeline was based on the assumption that the approval date for desonide gel is October 21, 2006 (rounded up to November 1, 2006 for easier calculations). The date for submission of the dose range finding studies is 6 months after the approval date for both studies (May 1, 2007). The date for submission of the dermal transgenic carcinogenicity study protocol is 6 months after submission of the 28-day dose range finding study (November 1, 2007). The date for submission of the 13-week mouse photosafety study protocol is 3 months after submission of the 21-day dose range finding study (August 1, 2007). The dates for starting the dermal transgenic carcinogenicity study and 13-week mouse photosafety study are 9 months and 6 months, respectively, after submission of the study protocol (August 1, 2008 and February 1, 2008, respectively). The dates for submitting the final study reports for the dermal transgenic carcinogenicity study and 13-week mouse photosafety study are 21 months and 12 months, respectively, after the study start date (May 1, 2010 and February 1, 2009, respectively).

Recommendations:

External Recommendations (to sponsor):

It is recommended that the following information be relayed to the sponsor for NDA 21-844.

The Division acknowledges receipt of the sponsor's proposed timeline for the nonclinical post-marketing commitments for Desonate (desonide) gel submitted to NDA 21-844 on August 30, 2006. The revised timeline appears acceptable. However, actual dates are needed for the timeline for tracking in the Post-marketing study database. Therefore, the Division recommends the following timeline for the nonclinical post-marketing commitments which incorporates dates into the timeline that correspond with the timeline proposed by the sponsor.

1. The applicant commits to conducting a dermal carcinogenicity study in Tg.AC mice with Desonate (desonide) gel.

4-week dose range finding study report
(plus TPA feasibility study):

By May 1, 2007

Study protocol submission:

By November 1, 2007

Study start date:

By August 1, 2008

Final report submission:

By May 1, 2010

-
2. The applicant commits to conducting a study to determine the photoco-carcinogenic potential of Desonate (desonide) gel (13-week photosafety study in mice).

3-week pilot study report (plus single dose SKH1-hr
mice studies for PK, irritancy and UVR response):

By May 1, 2007

Study protocol submission:

By August 1, 2007

Study start date:

By February 1, 2008

Final report submission:

By February 1, 2009

cc:

DDDP/DEP DIV DIR/KUKICH
DDDP/PHARM SUP/BROWN
DDDP/PHARM/HILL
DDDP/MO TL/LINDSROM
DDDP/MO/PAPADOPOULOS
DDDP/PM/JAIN

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/s/

Barbara Hill
9/12/2006 10:07:35 AM
PHARMACOLOGIST

Paul Brown
9/12/2006 10:26:40 AM
PHARMACOLOGIST