APPLICATION NUMBER:
21-978

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: 21-978
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: November 21, 2005
PRODUCT: (desonide) foam, 0.05%
INTENDED CLINICAL POPULATION: Corticosteroid responsive dermatoses
SPONSOR: Connectics Corporation
DOCUMENTS REVIEWED: Electronic eCTD 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: Melinda Bauerlien

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

I. Recommendations

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

B. Recommendation for nonclinical studies – A dermal carcinogenicity study conducted with foam and a study to determine the photoco-carcinogenic potential of foam 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
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-978
Review number: 1
Sequence number/date/type of submission: 000 / 11-21-05 / Original NDA submission
Information to sponsor: No
Sponsor and/or agent: Connetics Corporation
3290 West Bayshore Road
Palo Alto, CA 94303

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: Desonide foam, 0.05%
Generic name: Desonide foam, 0.05%
Code name: N/A
Chemical name: 11β, 16α, 17, 21-tetrahydroxyprogna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal
CAS registry number: 638-94-8
Molecular formula/molecular weight: C_{24}H_{32}O_{6} / 416.5
UV absorption: No significant absorption was noted for desonide alone or desonide foam, 0.05% over the measured spectrum from nm.
Reviewer: Barbara Hill

NDA No. 21-978

Structure:

[Chemical structure image]

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 67,825 (Desonide foam, atopic dermatitis, HFD-540)

Drug class: Corticosteroid, anti-inflammatory

Intended clinical population: Mild to moderate atopic dermatitis
Clinical formulation:

The composition of the foam, 0.05% is provided below.

<table>
<thead>
<tr>
<th>Component</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desonide</td>
<td></td>
</tr>
<tr>
<td>Cetyl alcohol, NF</td>
<td></td>
</tr>
<tr>
<td>Citric acid, USP</td>
<td></td>
</tr>
<tr>
<td>Cyclomethicone, NF</td>
<td></td>
</tr>
<tr>
<td>Isopropyl myristate, NF</td>
<td></td>
</tr>
<tr>
<td>Light mineral oil, NF</td>
<td></td>
</tr>
<tr>
<td>White petrolatum, USP</td>
<td></td>
</tr>
<tr>
<td>Phenoxyethanol*b</td>
<td></td>
</tr>
<tr>
<td>Polyoxyl 20 cetostearyl ether, NF</td>
<td></td>
</tr>
<tr>
<td>Potassium citrate monohydrate, USP</td>
<td></td>
</tr>
<tr>
<td>Propylene glycol, USP</td>
<td></td>
</tr>
<tr>
<td>Sorbitan monolaurate, NF*b</td>
<td></td>
</tr>
<tr>
<td>Purified water, USP</td>
<td></td>
</tr>
</tbody>
</table>

a  The sponsor submitted a literature report to support this non-compendial excipient in the original IND submission. It was determined that the literature report contained adequate information to qualify use of the phenoxyethanol excipient in the desonide foam, 0.05%.

b  The sponsor submitted a literature report to support this non-compendial excipient in the original IND submission. No genetic toxicology studies conducted with sorbitan monolaurate were described in the submitted literature reference. The sponsor stated in the IND submission that they will conduct the standard battery of ICH genetic toxicology studies with sorbitan monolaurate and provide the results with the NDA submission. It was determined that this is acceptable. The results of the genetic toxicology studies included in this NDA submission (reviewed in Section 2.6.4.4) indicate that sorbitan monolaurate is not genotoxic.

Note: Propane/butane is added as a propellant to the container at -%. The propellant is composed of approximately -% propane, -% butane and -% .

During the review of Connetics’ NDA 20-934 for betamethasone valerate foam, it was discovered that the butane/propane propellant could possibly contain the probable human carcinogen 1,3-butadiene at a specification of . The sponsor subsequently was able to lower this specification to 0.01 mole%. The sponsor also submitted a risk assessment for exposure to 1,3-butadiene from the propellant under exaggerated conditions of use. The results of this risk assessment showed that the specification of 0.01 mole% for dienes in the propellant appeared to ensure a level of butadiene in the product that did not exceed a cancer risk of $1 \times 10^{-6}$ except in extreme scenarios. The division decided that the specification of 0.01 mole% 1,3 butadiene was acceptable for this drug product.
The sponsor specified the level of \( \text{propane/butane propellant} \) for the desonide foam, 0.05% drug product as NMT \( \text{in the original IND submission} \). It was not clear if this is equivalent to \( \text{Yo as provided for the betamethasone valerate foam in NDA 20-934} \). It was requested that the sponsor assure that the level of \( \text{mole}\% \) in the propellant used for the desonide foam, 0.05% drug product. It was requested during the pre-NDA meeting conducted on September 12, 2005 that the sponsor provide the level of \( \text{mole}\% \) the propane/butane propellant used for the desonide foam drug product as mole\% to determine if the level was low enough to not pose a cancer risk. The sponsor has provided information in the NDA submission that indicates that the level of \( \text{mole}\% \) in the propane/butane propellant used for the desonide foam drug product is less than \( \text{which has been previously determined as acceptable} \). The sponsor states that the specification for \( \text{mole}\% \) in the propane/butane propellant in desonide foam is set to be no more than \( \text{The limit of \( \text{mole}\% \) is equivalent to \( \text{Therefore in desonide foam will not exceed \( \text{as recommended} \).} \)

Two leachable impurities that may be present in the finished product have been identified as \( \text{and } \). A risk assessment report was included in the NDA submission that focuses on the safety of these two leachable impurities in desonide foam. The risk assessment report includes a review and summary of the toxicology data available for \( \text{An evaluation of the adequacy of the submitted information is provided under the general toxicology section of this document (Section 2.6.1.1).} \) It is concluded that adequate data is available to support the safety of the worst case scenario estimate for the amounts of \( \text{that may be present in desonide foam.}

**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 foam dosage form of desonide, a line extension application. The sponsor has submitted a 505(b)(1) application for desonide foam, 0.05%. Connetics Corporation has obtained the right of reference to NDAs 17-010 and 17-426 (Tridesilon cream and Tridesilon ointment, respectively) to provide data to support a 505(b)(1) application. The right of reference letter from Clay Park Labs, Inc for NDAs 17-010 and 17-426 is included in this NDA submission.

A pre-IND/End of Phase 2 meeting was conducted with the sponsor on March 30, 2004. The IND for desonide foam was submitted on April 28, 2004. A pre-NDA meeting was conducted with the sponsor on September 12, 2005. This NDA submission is a totally electronic submission in CTD format.
Studies reviewed within this submission:

A) Studies incorporated by cross-reference to Tridesilon cream (NDA 17-010) and Tridesilon ointment (NDA 17-426)

Nonclinical Pharmacokinetic Studies:

1) Dermal absorption study conducted with desonide cream in rabbits  
2) Systemic distribution and excretion of desonide after intravenous administration in rats

Acute toxicology Studies:

1) Single dose subcutaneous rat toxicity study (desonide)  
2) Single dose oral rat toxicity study (desonide cream)  
3) Single dose dermal rabbit toxicity study (desonide cream)  
4) Single dose oral dog toxicity study (desonide cream)  
5) Single dose dermal rat toxicity study (desonide cream)  
6) Single dose oral rat toxicity study (desonide ointment)  
7) Single dose oral rabbit toxicity study (desonide ointment)

Repeat Dose Toxicity Studies:

1) 3 week dermal rabbit toxicity study (desonide cream)  
2) 30-day dermal repeat dose rabbit toxicity study (desonide ointment)  
3) 3 month dermal repeat dose rabbit toxicity study (desonide cream)

Reproductive and Developmental Toxicology Studies:

1) Dermal rat embryo-fetal development study (desonide cream)  
2) Dermal rabbit embryo-fetal development study (desonide cream)

B) Studies conducted by Connetics

Genetic Toxicology Studies (final study reports included in NDA submission):

1) Ames test (desonide)  
2) Ames test (sorbitan monolaurate, excipient)  
3) L5178Y tk⁺ mouse lymphoma assay (desonide)  
4) L5178Y tk⁺ mouse lymphoma assay (sorbitan monolaurate, excipient)  
5) Mouse micronucleus assay (oral {gavage}, desonide)  
6) Mouse micronucleus assay (oral {gavage}, sorbitan monolaurate, excipient)

Special Toxicity Studies (final study reports included with original IND submission):

1) Primary rabbit dermal irritation study (desonide foam)  
2) Primary rabbit ocular irritation study (desonide foam)
3) Guinea pig dermal sensitization study (modified Buhler design; desonide foam)

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 foam label under the “CLINICAL PHARMACOLOGY” section.

“The mechanism of anti-inflammatory activity of the topical corticosteroids 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

Two nonclinical pharmacokinetic studies were conducted with desonide under the Tridesilon cream/ointment NDAs. One study evaluated the absorption of desonide after topical administration of desonide cream to rabbits. A radiolabled (\(^{14}\)C-desonide, 0.263 \(\mu\)Ci/g cream)
preparation of desonide cream, 0.01% was topically administered to occluded (for 8 hours) and non-occluded intact and abraded skin treatment sites of male rabbits. Under non-occlusive conditions, 6.47% and 6.99% of the topically administered desonide was absorbed after topical administration of desonide cream to intact and abraded skin, respectively. Occlusion of the application site for 8 hours did not significantly increase the absorption of desonide in animals with intact skin, but the absorption of desonide in animals with occluded, abraded skin was increased to 14.94%.

The second study evaluated the distribution and excretion of desonide after intravenous administration to male rats. $^{14}$C-labeled desonide (specific activity 2.133 μCi/mg) was prepared either in propylene glycol (for tissue distribution study) or in an undenatured alcohol and isotonic saline solution (excretion study). Both preparations were administered in a volume of 0.2 ml/200 g body weight. Twenty-one rats were assigned to the distribution study and 3 animals were sacrificed at each of the following time points: 0.5, 1, 2, 4, 8, 16, or 24 hours after desonide administration (5 mg/kg). Tissues were collected for subsequent analysis. Ten rats were used in the excretion study. Treated animals were placed in metabolism cages after desonide administration (5 mg/kg). Urine samples were collected at 2, 4, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours; feces were collected at 24-hour intervals through 96 hours. Peak tissue levels were maximal between 30 minutes and 1 hour after desonide administration. The highest amount of radioactivity was found in the liver. The other tissues evaluated, listed in decreasing order of $^{14}$C level, were adrenal, kidney, dorsal aorta, plasma, mesenteric fat, lung, peri-renal fat, heart, epididymal fat, gastrocnemius muscle, spleen, and brain. The mean biological half-life of the drug based on the $^{14}$C level in these tissues was 4.26 hours. By 96 hours after drug administration, 76.16% of the dose was excreted, 67% via the feces and the remainder in the urine.

The following information concerning desonide pharmacokinetics activity is contained in the proposed foam label under the “CLINICAL PHARMACOLOGY; Pharmacokinetics” section.

“Topical corticosteroids can be absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the product formulation and the integrity of the epidermal barrier. Occlusion, inflammation and/or other disease processes in the skin may also increase percutaneous absorption. The use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids may be necessary due to the fact that circulating levels are often below the level of detection. Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. They are metabolized, primarily in the liver, and are then excreted by the kidneys. Some corticosteroids and their metabolites are also excreted in the bile.”

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 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 foam, 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

The sponsor submitted two literature reference articles in the original IND submission for desonide foam (IND 67,825; submitted on April 28, 2004) to support the use of the two non-compendial excipients in the drug product. The titles of the two articles are provided below.

1) Final report on the safety assessment of phenoxyethanol, Journal of the American College of Toxicology, Volume 9, Number 2, 1990 (Mary Ann Liebert, Inc., Publishers)

2) Final report on the safety assessment of sorbitan stearate, sorbitan laurate, sorbitan sesquioleate, sorbitan oleate, sorbitan tristearate, sorbitan palmitate and sorbitan trioleate, Journal of the American College of Toxicology, Volume 4, Number 3, 1985 (Mary Ann Liebert, Inc., Publishers)

The information contained in these two literature references was reviewed in the original IND review that was entered into DFS on May 24, 2004. Refer to this review if additional detail is needed. It was determined after review of the information contained in both literature references that the results of the studies described in the first submitted reference article appeared adequate to qualify use of the phenoxyethanol excipient in the desonide foam, 0.05%. No additional nonclinical toxicology studies were recommended for the phenoxyethanol excipient.
No genetic toxicology studies conducted with sorbitan monolaurate were described in the second submitted literature reference. The sponsor stated in the original IND submission that they will conduct the standard battery of ICH genetic toxicology studies with sorbitan monolaurate and provide the results with the NDA submission. It was determined that this was acceptable. The sponsor has included the final study reports for the genetic toxicology studies conducted with sorbitan monolaurate in this NDA submission. The results of these studies are reviewed under Section 2.6.4.4 in this document and a summary of the results of these studies are provided under the genetic toxicology subheading of this section of the document.

General toxicology:

Several single dose toxicity studies were conducted with desonide under the Tridesilon cream/ointment NDAs. Single dose toxicity studies have been conducted with desonide in three species (rat, rabbit and dog) by three routes of administration (oral, subcutaneous and topical).

The acute systemic toxicology of desonide has been evaluated in rats after subcutaneous administration. The subcutaneous LD$_{50}$ 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. The acute oral toxicology of the desonide ointment formulation was evaluated in rats. Rats were orally administered 0.05% desonide ointment (4.25 g ointment/kg). No treatment related clinical effects or 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 LD$_{50}$ 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 LD$_{50}$ for desonide cream 0.2% was >16 g cream/kg in rabbits.

The dermal toxicity of desonide cream or ointment after repeated topical doses from 3 to 13 weeks was evaluated in three nonclinical studies conducted in rabbits, with intact and abraded skin treatment sites. A 3 week dermal repeat dose toxicology study was conducted in rabbits with a desonide cream formulation. Rabbits (3/sex/dose) were topically treated with 2 g cream/kg of 0% (vehicle cream), 0.05%, 0.1% or 0.2% desonide cream. Topical applications were applied once daily, 5 days/week, onto the shaved intact or abraded back skin of rabbits for three consecutive weeks. The dermal reactions included very slight to moderate erythema and
very slight edema noted in vehicle and desonide cream treated animals. No dose related increase in dermal reactions was noted in this study. Treatment related systemic effects included one death (high dose male) and characteristic changes in different organs at the end of treatment indicative of corticosteroid toxicity (increased glycogen in the liver, adrenal atrophy, lymph node atrophy, spleen congestion and thymus atrophy). The results of this study indicated some systemic effects for desonide after repeat dose topical administration of relatively high doses of the desonide cream.

A 30 day dermal repeat dose toxicology study was conducted in rabbits with a desonide ointment formulation. Rabbits (3/sex/dose) received daily dermal doses of 0.2, 0.6 or 2 g cream/kg of a desonide ointment 0.05% formulation or 2 g/kg of the ointment vehicle. Test article was administered to intact or abraded treatment sites once daily for 30 days. Animals wore Elizabethan-type neck collars to prevent ingestion of test article. No deaths occurred during the study. Slight to moderate erythema was noted at the treatment sites of all dose groups. Dermal responses became progressively less severe after repeated applications. No treatment related effects on body weight, food consumption or clinical chemistry parameters were noted in this study. Possible treatment related effects on macroscopic parameters included pulmonary congestion (noted in 11 rabbits spread across the dose groups including 4 from the ointment control group), renal congestion (noted in 1 or 2 animals from each of the 4 groups) and congestion of the liver (noted in 3 animals from the high-dose group). Sloughing mucosa in the small intestine was noted in a number of animals from the low-, mid- and high-dose groups. Treatment and dose dependent effects on organ weights were noted in this study. Liver weight and liver weight ratios were increased in high-dose males and in mid- and high-dose females. Adrenal weight and weight ratios were decreased at all dose levels in both sexes. No histopathologic changes were observed in the adrenals. A slight increase in centrolobular distribution of intracytoplasmic lipid in the liver was noted in a number of the desonide ointment treated animals, which may have been the cause of the increase in liver weights. The results of this study indicated some systemic effects for desonide after repeat dose topical administration of relatively high doses of the desonide ointment.

A 13 week dermal repeat dose toxicology study was conducted in rabbits with a desonide cream formulation. Rabbits (3/sex/dose) received daily dermal doses of 0.2, 0.6 or 2 g cream/kg of a desonide cream 0.05% formulation or 2 g/kg of the cream base. Test article was administered to intact or abraded treatment sites once daily for 13 weeks. Animals wore Elizabethan-type neck collars to prevent ingestion of test article. One high dose female rabbit died in this study. Minimal irritation was noted in vehicle and test article treated animals. No treatment related effects on clinical signs or food consumption was noted in this study. No treatment related effects on body weight were 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. Increased liver weights were noted in mid dose males and high dose animals, decreased adrenal weights were noted in low, mid and high dose animals, decreased gonad weight was noted in high dose animals and decreased spleen weight was noted in high dose females. No treatment related effects on histopathological parameters were noted in this study.
Overall, the results of the dermal toxicology studies conducted to support desonide cream/ointment indicate that some systemic effects are noted after repeat dose topical administration of relatively high doses of desonide cream/ointment. The toxicity profile noted was characteristic for corticosteroids. No repeat dose dermal toxicology studies have been conducted with desonide foam. However, it is anticipated that the toxicity profile of desonide foam will be similar to desonide cream/ointment. Therefore, no additional general toxicology studies are recommended for desonide foam.

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 test (Ames assay), an in vitro mammalian cell mutagenesis assay (L5178Y/TK⁺ mouse lymphoma assay) and an in vivo mouse micronucleus assay. It is recommended that the genotoxicity information for desonide be incorporated into the desonide foam label. The recommended wording for this section of the label is provided in the “Recommendations” section of this review.

Sorbitan monolaurate was evaluated for genotoxicity in a battery of in vitro and in vivo genetic toxicology studies. Sorbitan monolaurate was negative in an in vitro bacterial mutagenesis test (Ames assay), an in vitro mammalian cell mutagenesis assay (L5178Y/TK⁺ mouse lymphoma assay) and an in vivo mouse micronucleus assay.

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

Carcinogenicity:

No nonclinical dermal carcinogenicity or photocarcinogenicity 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 photocarcinogenic potential of desonide foam, 0.05% were recommended as phase 4 commitments.

The sponsor states in the NDA submission that they plan to conduct a dermal carcinogenicity study in a single species and a photocarcinogenicity study in a single species, with desonide foam as a post-marketing commitment. The sponsor further states that the dose-ranging studies will be initiated within 1 year of the product launch of desonide foam in the US market, and the protocols for the definitive studies will be submitted to the CAC within 1 year after completion of the dose-ranging studies. 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 foam is September 21, 2006 (rounded up to October 1, 2006 for easier calculations). The date for submission of the 90-day dose range finding study is 18 months after the approval
date for both studies (April 1, 2008). The date for submission of the study protocol is 6 months after submission of the 90-day dose range finding study for both studies (October 1, 2008). The date for starting both studies is 8 months after submission of the study protocol (June 1, 2009). The date for submitting the final study reports for the traditional dermal carcinogenicity study and photoco-carcinogenicity study is 3.5 years and 2.5 years, respectively, after the study start date (December 1, 2012 and December 1, 2011, respectively). These timelines have been used for previous recommendations for traditional dermal carcinogenicity and photoco-carcinogenicity studies for corticosteroids (e.g., Vanos {flucinonide} cream, NDA 21-758, approved February 11, 2005).

Reproductive toxicology:

Two dermal embryo-fetal 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 Tridesilon cream/ointment, 0.05% label for the reproductive and developmental toxicity potential of desonide. Tridesilon cream/ointment, 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 topical corticosteroids.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
Dermal embryofetal development studies have been conducted in rats and rabbits with Tridesilon 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 Tridesilon 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 foam 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.

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 foam 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 foam.

Special toxicology:

Desonide foam, 0.05% was a minimal dermal and ocular irritant in rabbits and did not elicit a sensitization response in a modified buhler design assay conducted in guinea pigs. These studies were reviewed under the original IND submission.

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

Review of risk assessment for —and (Module 4, Section 4.2.3.7.1)

Two leachable impurities that may be present in the finished product have been identified as — and —. A risk assessment report was included in the NDA submission that focuses on the safety of these two possible leachables in desonide foam. The risk assessment report includes a review and summary of the toxicology data available for — and —. The title of the risk assessment report is “Risk assessment of — (‘—’) and —, as potential leachable impurities in a topical pharmaceutical product”. The risk assessment report was submitted for the sponsor by —. This report was written by — with a completion date of September 29, 2005.
4 Page(s) Withheld

☑ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(4) Draft Labeling

☐ § 552(b)(5) Deliberative Process
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

Genetic toxicology study #1

Study title Desonide: Bacterial Reverse Mutation Test

Key findings: Desonide was not mutagenic in the Ames assay, under the conditions of this study.

Study no.: 04-04-001A
Volume #, and page #: Module 4, Section 4.2.3.3.1.1
Conducting laboratory: 5-5-04
Date of study initiation: Yes
GLP compliance: Yes
QA reports: Desonide, Lot# 04-04-001
Drug, lot #, and % purity: DMSO
Vehicle: DMSO

Methods

Strains/species/cell line: Salmonella typhimurium strains TA 97a, TA98, TA100 and TA1535; Escherichia coli strain WP2 uvrA

Doses used in definitive study: 100, 500, 1000, 2500 and 5000 μg/plate (± S9; S9 derived from Aroclor 1254 induced rat liver homogenate); 3 plates/dose

Basis of dose selection: Dose range finding study performed with all test strains (± S9). Concentrations of 5, 10, 50, 100, 500, 1000, 2500 and 5000 μg/plate desonide were evaluated for cytotoxicity (2 plates/dose). Toxicity expressed as reductions in revertant counts was noted at 1000 μg/plate and higher. The high dose in the definitive study was set at 5000 μg/plate for all test strains.

Negative controls: DMSO
Positive controls: Appropriate positive controls were used in this Ames test.

Incubation and sampling times: Plates were incubated at 37 ± 2°C for 48 hrs after treatment. Plates were counted for colony formation by hand after completion of the incubation period.

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 Desonide: L5178Y TK+/- mouse lymphoma assay

Key findings: Desonide was negative in the L5178Y TK+/- mouse lymphoma assay, with and without S9 activation, under the conditions of this assay.

Study no.: 04-04-001MLA
Volume #, and page #: Module 4, Section 4.2.3.3.1.2
Conducting laboratory: 5-31-04
Date of study initiation: Yes
GLP compliance: Yes
QA reports: Desonide, Lot# 04-04-001
Drug, lot #, and % purity: DMSO
Vehicle:

Methods

Strains/species/cell line: L5178Y TK+/- mouse lymphoma cells (3.7.2C clone)
**Doses used in definitive study:**
3 hr incubation: 6.25, 12.5, 25, 50, 100, 200, 400, 800 and 1600 µg/ml (± S9; S9 derived from 6-processed induced rat liver homogenate); 2/dose
20 hr incubation: 6.25, 12.5, 25, 50, 100, 200, 400 and 800 µg/ml (-S9); 2/dose

**Basis of dose selection:**
Cytotoxicity was determined by relative total growth based on cell densities taken after treatment, after the 24 hour expression period and the 48 hour expression period. No toxicity was noted over the concentration range tested for the 3 hr incubation, but was noted at concentrations of 800 µg/ml and higher. Toxicity was noted at 200 µg/ml and above in the 20 hr incubation and was noted at the 800 µg/ml concentration.

**Negative controls:**
DMSO

**Positive controls:**
Methyl Methanesulfonate (-S9)
Cyclophosphamide (+S9)

**Incubation and sampling times:**

Cells suspensions were incubated with test article for 3 hour (±S9) or 20 hour exposure (-S9) at 37 °C. Cell suspensions were rinsed, resuspended in culture medium and maintained at 37 °C for a 2 day expression period. Cell suspensions were then cultured either on viable count control plates or trifluorothymidine plates (the selective agent). The plates were incubated at 37 °C for 10 – 14 days. Plates were counted for colony formation manually after completion of the incubation period.

**Results**

**Study validity:**

A test article was considered to be positive if the mutant frequency at any concentration with 10% or greater growth was at least two times greater than the mutant frequency in the concurrent vehicle control and demonstrated a concentration related increase in mutant frequency.

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:**

Desonide did not produce a significant increase in the total mutant frequency above negative control levels with or without metabolic activation, under the conditions of this assay.
Genetic toxicology study #3

Study title: Desonide: In vivo micronucleus in mouse bone marrow

Key findings: Desonide was negative in the in vivo mouse micronucleus assay, under the conditions of this study.

Study no.: 04-04-001MN
Volume #, and page #: Module 4, Section 4.2.3.3.2.1
Conducting laboratory:
Date of study initiation: 9-17-04
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: Desonide, Lot# 04-04-001
Vehicle: Carboxymethylcellulose

Methods

Strains/species/cell line: CD-1 mice; 8-9 weeks; males: 26.5-36.0 g; females: 23.9-29.5 g; 5/sex/dose/timepoint

Doses used in definitive study: 0, 800, 1400 and 2000 mg/kg desonide; oral (gavage); dose volume: 10 ml/kg

Basis of dose selection: Single oral (gavage) doses of 1000 and 2000 mg/kg desonide, were administered to mice (1/sex/dose) in a dose range finding study. This dose range finding study indicated that a maximum dose of 2000 mg/kg was well tolerated. Therefore, doses of 800, 1400 and 2000 mg/kg were selected for the definitive study.

Negative controls: Carboxymethylcellulose

Positive controls: Cyclophosphamide (70 mg/kg); oral (gavage); vehicle: water; dose volume: 10 ml/kg

Incubation and sampling times: Single oral (gavage) doses of desonide 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 above concurrent vehicle control values 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:

A moderate decrease in body weight was noted in high dose animals. Bone marrow toxicity was noted as decreased PCE fraction in mid and high dose groups. No significant increase in micronucleated PCEs in desonide treated groups compared to corresponding vehicle control was noted in this study.

Genetic toxicology study #4

Study title: Sorbitan Monolaurate: Bacterial Reverse Mutation Test

Key findings: Sorbitan Monolaurate was not mutagenic in the Ames assay, under the conditions of this study.

Study no.: 04-04-002A
Volume #, and page #: Module 4, Section 4.2.3.3.1.3
Conducting laboratory: 5-5-04
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: Sorbitan monolaurate, Lot# 04-04-002
Vehicle: DMSO

Methods

Strains/species/cell line: Salmonella typhimurium strains TA 97a, TA98, TA100 and TA1535; Escherichia coli strain WP2 uvrA
Doses used in definitive study: 0.5, 1, 5, 10, 50, 100, 500 and 1000 µg/plate (± S9; S9 derived from induced rat liver homogenate); 3 plates/dose

Basis of dose selection: Dose range finding study performed with all test strains (± S9). Concentrations of 5, 10, 50, 100, 500, 1000, 2500 and 5000 µg/plate sorbitan monolaurate were evaluated for cytotoxicity (2 plates/dose). Toxicity expressed as moderate to severe reduction in or completely absent background lawn was noted at 1000 µg/plate and higher.

Negative controls: DMSO

Positive controls: Appropriate positive controls were used in this Ames test.

Incubation and sampling times: Plates were incubated at 37 ± 2°C for 48 hrs after treatment. Plates were counted for colony formation by hand after completion of the incubation period.

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 #5

Study title Sorbitan monolaurate: L5178Y TK⁺/⁻ mouse lymphoma assay

Key findings: Sorbitan monolaurate was negative in the L5178Y TK⁺/⁻ mouse lymphoma assay, with and without S9 activation, under the conditions of this assay.

Study no.: 04-04-002MLA
Volume #, and page #: Module 4, Section 4.2.3.3.1.4
Conducting laboratory: 
Date of study initiation: 5-24-04
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: Sorbitan monolaurate, Lot# 04-04-002
Vehicle: DMSO

Methods

Strains/species/cell line: L5178Y TK<sup>++</sup> mouse lymphoma cells (3.7.2C clone)

Doses used in definitive study: 3 hr incubation: 5, 10, 20, 50, 100, 200, 500, 1000 and 2500 µg/ml (± S9; S9 derived from induced rat liver homogenate); 2/dose

20 hr incubation: 2.5, 5, 10, 20, 50, 100, 200 and 500 µg/ml (-S9); 2/dose

Basis of dose selection: Cytotoxicity was determined by relative total growth based on cell densities taken after treatment, after the 24 hour expression period and the 48 hour expression period. Toxicity was noted at concentrations of 500, 1000 and 2500 µg/ml for the 3 hr incubation and at 200 and 500 µg/ml in the 20 hr incubation.

Negative controls: DMSO

Positive controls: Methyl Methanesulfonate (-S9) Cylocphosphamide (+S9)

Incubation and sampling times:

Cells suspensions were incubated with test article for 3 hour (±S9) or 20 hour exposure (−S9) at 37 °C. Cell suspensions were rinsed, resuspended in culture medium and maintained at 37 °C for a 2 day expression period. Cell suspensions were then cultured either on viable count control plates or trifluorothymidine plates (the selective agent). The plates were incubated at 37 °C for 10 – 14 days. Plates were counted for colony formation manually after completion of the incubation period.
Results

Study validity:

A test article was considered to be positive if the mutant frequency at any concentration with 10% or greater growth was at least two times greater than the mutant frequency in the concurrent vehicle control and demonstrated a concentration related increase in mutant frequency.

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:

Sorbitan monolaurate did not produce a significant increase in the total mutant frequency above negative control levels, with or without metabolic activation, under the conditions of this assay.

Genetic toxicology study #6

Study title  Sorbitan monolaurate: In vivo micronucleus in mouse bone marrow

Key findings:  Sorbitan monolaurate was negative in the in vivo mouse micronucleus assay, under the conditions of this study.

Study no.: 04-04-002MN
Volume #, and page #: Module 4, Section 4.2.3.3.2.2
Conducting laboratory: 9-9-04
Date of study initiation: 9-9-04
GLP compliance: Yes
QA reports: Yes
Drug, lot #, and % purity: Sorbitan monolaurate, Lot# 04-04-002
Vehicle: Corn oil

Methods

Strains/species/cell line: CD-1 mice; 7-9 weeks; males: 30.5-35.1 g; females: 20.4-27.2 g; 5/sex/dose/timepoint

Doses used in definitive study: 0, 800, 1400 and 2000 mg/kg sorbitan monolaurate; oral (gavage); dose volume: 10 ml/kg

Basis of dose selection: Single oral (gavage) doses of 1000 and 2000 mg/kg sorbitan monolaurate, were administered to mice (1/sex/dose) in a dose range finding study. This dose range finding study indicated
that a maximum dose of 2000 mg/kg was well tolerated. Therefore, doses of 800, 1400 and 2000 mg/kg were selected for the definitive study.

**Negative controls:** Corn oil

**Positive controls:** Cyclophosphamide (70 mg/kg); oral (gavage); vehicle: water; dose volume: 10 ml/kg

**Incubation and sampling times:** Single oral (gavage) doses of sorbitan monolaurate 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 above concurrent vehicle control values 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 signs of toxicity were noted in this study. No significant increase in micronucleated PCEs in sorbitan monolaurate treated groups compared to corresponding vehicle control was noted in this study.

**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

Desonide and sorbitan monolaurate were negative in an ICH battery of genotoxicity studies. 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 foam 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 foam and a study to determine the photoco-carcinogenic potential of foam as Phase 4 commitments.

The sponsor has provided adequate data to address any potential safety concerns for the - and -leachables that may be contained in the desonide foam. The sponsor has also provided adequate information to assure that the level of - butadiene in the propane/butane propellant used for the desonide foam, 0.05% drug product is -than NMT - ppm, a level previously determined to be low enough to not pose a cancer risk.

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 21-978 for foam, 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 foam, 0.05% label.
The sponsor has agreed to conduct a dermal carcinogenicity study with --- foam and a study to determine the photoco-carcinogenic potential of --- foam 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 21-978, at this time.

Recommendations:

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

It is recommended that the following nonclinical Post-marketing commitment information be included in an approval letter for --- foam, 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 --- (desonide) foam.

| 90-day dose range-finding study: | By April 1, 2008 |
| Study protocol submission: | By October 1, 2008 |
| Study start date: | By June 1, 2009 |
| Final report submission: | By December 1, 2012 |

2. The applicant commits to conducting a study to determine the photoco-carcinogenic potential of --- (desonide) foam.

| 90-day dose range-finding study: | By April 1, 2008 |
| Study protocol submission: | By October 1, 2008 |
| Study start date: | By June 1, 2009 |
| Final report submission: | By December 1, 2011 |

Suggested labeling:

The nonclinical portions of the --- foam, 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 --- foam, 0.05% label.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term animal studies have not been performed to evaluate the carcinogenic or photoco-carcinogenic potential of --- foam or the effect on fertility of desonide.
Desonide revealed no evidence of mutagenic potential based on the results of two in vitro
genotoxicity tests (Ames assay, mouse lymphoma cell assay) and an in vivo genotoxicity test
(mouse micronucleus assay).

Pregnancy: Teratogenic Effects: Pregnancy Category C: 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.

Dermal embryofetal development studies were conducted in rats and rabbits with a desonide
cream, 0.05% formulation. Topical doses of 0.2, 0.6 and 2.0 g cream/kg/day of a desonide
cream, 0.05% formulation or 2.0 g/kg of the cream base were administered topically to pregnant
rats (gestational days 6 – 15) and pregnant rabbits (gestational days 6 – 18). Maternal body
weight loss was noted at all dose levels of the desonide cream, 0.05% formulation in rats and
rabbits. Teratogenic effects characteristic of corticosteroids were noted in both species. The
desonide cream, 0.05% formulation was teratogenic in rats at topical doses of 0.6 and 2.0 g
cream/kg/day and in rabbits at a topical dose of 2.0 g cream/kg/day. No teratogenic effects were
noted for the desonide cream, 0.05% formulation at a topical dose of 0.2 g cream/kg/day in rats
and at a topical dose of 0.6 g cream/kg/day in rabbits. These doses (0.2 g cream/kg/day and 0.6
g cream/kg/day) are similar to the maximum recommended human dose based on body surface
area comparisons.

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 Foam is administered to a
nursing woman.

Signatures (optional):

Reviewer Signature

Supervisor Signature Concurrence Yes No
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
7/13/2006 11:33:27 AM
PHARMACOLOGIST
Nonclinical post-marketing commitments to be relayed to sponsor

Paul Brown
7/13/2006 12:45:06 PM
PHARMACOLOGIST