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*APPLICATION NUMBER:*  
**22-013**

**PHARMACOLOGY REVIEW**

## Pharmacology/Toxicology Supervisory Memorandum

**NDA number: 22-013**

Sequence number/date/type of submission: 000 / 16 March 2006 / original submission

Sponsor and/or agent: Connetics

Supervisor name: Paul C. Brown

Division name: Division of Dermatology and Dental Products

Date: November 14, 2006

Drug: clobetasol foam, 0.05%

Drug class: corticosteroid

Indication: corticosteroid-responsive dermatoses

### Comment:

This memorandum is to clarify that the pharm/tox review and recommendation for approval of this NDA are not relying upon the Agency's previous finding of safety or efficacy for Clobex Shampoo (0.05% clobetasol propionate, NDA 21-644).

This NDA was submitted under section 505(b)(2) of the FD&C Act. The sponsor established a clinical bridge to Temovate Ointment (0.05% clobetasol propionate, NDA 19-323). The sponsor did not establish a clinical bridge to any other listed drug product.

The sponsor states in the NDA that some of the information used in the proposed labeling was derived from the labeling of Clobex Shampoo. The wording proposed by the sponsor for the

The pharm/tox reviewer recommended labeling that does not contain a description of the ~~\_\_\_\_\_~~. This ~~\_\_\_\_\_~~ is not necessary for approval of the NDA. The pharm/tox proposed labeling consists only of information from studies conducted by the sponsor or from the Temovate Ointment labeling.

The pharm/tox review and recommendation for approval of this NDA are not relying upon the Agency's previous finding of safety or efficacy for the Clobex Shampoo product.

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/s/  
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Paul Brown  
11/14/2006 01:53:23 PM  
PHARMACOLOGIST

memo to address 505(b)(2) issue

Susan Walker  
11/20/2006 04:08:01 PM  
DIRECTOR

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Clobetasol propionate, a synthetic corticosteroid, is an analog of prednisolone with a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity. It has anti-inflammatory, antipruritic and vasoconstrictive activity. The mechanism of action of corticosteroids is thought to be the induction of phospholipase A2 inhibitory proteins. These proteins inhibit the release of arachidonic acid, a precursor to immunomodulators like leukotrienes and prostaglandins. Studies performed with Primolux™ foam indicate it is in the super-high range of potency as compared with other topical corticosteroids. Treatment beyond 2 weeks is not recommended, due to the product's potential to suppress the hypothalamic-pituitary-adrenal axis. Use in pediatric patients under 12 is not recommended.

C. Nonclinical safety issues relevant to clinical use

There are no nonclinical safety issues relevant to the clinical use of Primolux™.

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## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number:** 22-013

**Review number:** 1

**Sequence number/date/type of submission:** N-000/16-Mar-2006

**Information to sponsor:** Yes ( X ) No ( )

**Sponsor and/or agent:** Connetics Corporation

**Manufacturer for drug substance:** \_\_\_\_\_

**Reviewer name:** Carmen D. Booker, Ph.D.

**Division name:** Dermatology and Dental Products

**HFD #:** 540

**Review completion date:** October 25, 2006

**Drug:**

Generic name: clobetasol propionate

Chemical name: (11 $\beta$ ,16 $\beta$ )-21-chloro-9-fluoro-11-hydroxy-16-methyl-17(1-oxopropoxy)-pregna-1,4-diene-3,20-dione

CAS registry number: 25122-46-7

Molecular formula/molecular weight: C<sub>25</sub>H<sub>32</sub>ClFO<sub>5</sub> / 466.98

**Relevant INDs/NDAs/DMFs:** IND 67,818; NDA 19-323; NDA 21-142; IND 55,805; NDA 19-322, NDA 19-966; NDA 20-337 and NDA 20-340

**Drug class:** Corticosteroid

**Intended clinical population:** Patients with inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

**Clinical formulation:** Topical (ethanol-free) foam containing 0.05% clobetasol propionate

Component	Ethanol-free foam (%w/w)
Clobetasol propionate, USP	0.05
White petrolatum, USP	
Light mineral oil, NF	
Isopropyl myristate, NF	
Cyclomethicone, NF	
Cetyl alcohol, NF	
Sorbitan monolaurate, EP or NF	

Propylene glycol, USP	r	1
Citric acid, USP	L	2

**Route of administration:** Topical

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

**Data reliance:** Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-013 are owned by Connetics Corporation or are data for which Connetics Corporation has obtained a written right of reference. Any information or data necessary for approval of NDA 22-013 that Connetics Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Connetics Corporation does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-013.

**Studies reviewed within this submission:**

Safety Assessment of Phenoxyethanol, 1990.

Safety Assessment of Sorbitan Monolaurate, 1985.

Study Report 04-04-002A. Sorbitan Monolaurate: Bacterial Reverse Mutation Test: Plate Incorporation and Preincubation Method for Liquids.

Study Report 04-04-003A. Clobetasol Propionate: Bacterial Reverse Mutation Test: Plate Incorporation and Preincubation Method for Solids.

Study Report 04-04-002MN. Sorbitan Monolaurate: *In vivo* Micronucleus in Mouse Bone Marrow for Liquids: Single Administration.

Study Report 04-04-002MLA. Sorbitan Monolaurate: L5178Y TK+/- Mouse Lymphoma Assay for Liquids.

Study Report 04-04-003MLA. Clobetasol Propionate: L5178Y TK+/- Mouse Lymphoma Assay for Solids.

**The following studies were submitted to IND 67,818 and previously reviewed by Paul Brown, Ph.D. on May 25, 2004. Excerpts from Dr. Brown's review are included in this review.**

Comparison of skin penetration of clobetasol propionate from some formulations *in vitro*

using the human skin model (Study SL03-16)

A primary eye irritation study in rabbits with Olux-E aerosol foam (Study 3600.17)

A primary skin irritation study in rabbits with Olux-E aerosol foam (Study 3600.18)

**The following study was submitted to IND 67,818 and previously reviewed by Carmen D. Booker, Ph.D. on September 21, 2005. Excerpts from Dr. Booker's review are included in this review.**

Study Report 04-04-003MN. Clobetasol Propionate: *In vivo* Micronucleus in Mouse Bone Marrow for Solids: Single Administration.

**Studies not reviewed within this submission: None**

## 2.6.2 PHARMACOLOGY

### 2.6.2.1 Brief summary

Clobetasol propionate, a synthetic corticosteroid, is an analog of prednisolone with a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity. It has anti-inflammatory, antipruritic and vasoconstrictive activity. The mechanism of action of corticosteroids is thought to be the induction of phospholipase A2 inhibitory proteins. These proteins inhibit the release of arachidonic acid, a precursor to immunomodulators like leukotrienes and prostaglandins. Studies performed with Primolux™ foam indicate it is in the super-high range of potency as compared with other topical corticosteroids. Treatment beyond 2 weeks is not recommended, due to the product's potential to suppress the hypothalamic-pituitary-adrenal axis. Use in pediatric patients under 12 is not recommended.

### 2.6.2.2 Primary pharmacodynamics

Mechanism of action: Clobetasol propionate exerts its effects via multiple pathways, including inhibition of the arachidonic acid cascade and cytokine production. Clobetasol propionate is believed to affect these pathways through the induction of phospholipase A2 inhibitory proteins.

Drug activity related to proposed indication: Similar to other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic and vasoconstrictive properties; therefore, it is useful in the treatment of inflammatory and pruritic lesions associated with dermatoses.

### 2.6.2.3 Secondary pharmacodynamics

No new data or information on the secondary pharmacodynamics of clobetasol propionate were submitted.

Systemic absorption of topical corticosteroids can cause adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.

#### **2.6.2.4 Safety pharmacology**

No new safety pharmacology studies were submitted with this NDA. The literature and previous clinical experience with Temovate<sup>®</sup> and Olux<sup>®</sup> Foam suggest that there are no safety pharmacology concerns associated with clobetasol propionate.

#### **2.6.2.5 Pharmacodynamic drug interactions**

The labeling for Primolux<sup>™</sup> will include the same information on precautions regarding drug interactions as the approved product labeling for Olux<sup>®</sup> Foam.

### **2.6.3 PHARMACOLOGY TABULATED SUMMARY**

No new pharmacology or safety pharmacology studies have been conducted on clobetasol propionate. See summaries above.

### **2.6.4 PHARMACOKINETICS/TOXICOKINETICS**

#### **2.6.4.1 Brief summary**

Nonclinical studies, *in vivo and in vitro*, have shown that clobetasol propionate is absorbed through animal and human skin. In general, percutaneous absorption of clobetasol propionate is increased by occlusion. Clearance of clobetasol propionate is mainly by the liver, bile and feces. The new ethanol-free (emollient) foam dose not appear to produce greater penetration compared to the previous foam formulation in the *in vitro* human skin model.

#### **2.6.4.2 Methods of Analysis**

Methods of analysis are discussed within individual study reviews. Please see reviews associated with IND 67,818 and NDA 19-323.

#### **2.6.4.3 Absorption**

Topical corticosteroids are absorbed from healthy intact skin. Percutaneous absorption can be altered by many factors, including the formulation of the vehicle, the integrity of the epidermal barrier and the use or lack of use of occlusive dressings. Other disease processes may also affect percutaneous absorption.

**Study title: Comparison of skin penetration of clobetasol propionate from some formulations *in vitro* using the human skin model**

**Study number:** SL03-16

**Vol. #2, page #286**

**Conducting laboratory and location:** Connetics Corp., Palo Alto, CA

**Date of study initiation:** 22 August 2003

**GLP compliance:** No

**QA-Report:** No

**Drug, lot#, and % purity:**

1. Clobetasol propionate emollient foam, 0.05% [Olux-E (PG)], Lot No. 367-44
2. Olux Foam, 0.05%, Lot No. 1H964 (previous foam formulation)
3. Temovate Cream, 0.05%, Lot No. 1H372
4. Temovate E-cream, 0.05%, Lot No. 1C284
5. Temovate Scalp Application, 0.05%, Lot No. 1L722
6. Temovate Ointment, 0.05%, Lot No. 1H371
7. Embeline E (cream) Emollient, 0.05%, Lot No. SBAD

**Methods:** Skin from a single human donor was sliced to approximately 0.25mm thickness and placed on diffusion cells with an exposure area of 0.64 cm<sup>2</sup>. Phosphate buffered isotonic saline was used as the receptor fluid. Penetration of tritiated water was used to test the integrity of each skin section. Each test material was warmed to 40-50°C and 500 µl of each was spiked with 50 µCi of [<sup>3</sup>H]-clobetasol propionate. The warming causes the liquefaction of the formulations. Approximately 10 µl of each formulation was applied to the skin in each cell (3 cells/formulation). The receptor fluid was sampled every 4 hours over a 24 hour period. At the end of the 24 hours period the skin surface was wiped and washed with acetonitrile and tape stripped. Epidermis and dermis were separated. Radioactivity in the different samples was quantified by liquid scintillation counting.

**Results, Conclusions and Comments:** The greatest penetration to the receptor appeared to occur with the Temovate<sup>®</sup> ointment. The percentage of the applied drug that penetrated to the receptor fluid appears similar for the two foam products and is similar to the results with the cream products. The previous foam formulation appeared to produce the greatest level of drug in the epidermis. The total recovery for some of the products was low and the reason for this low recovery is not clear. This could substantially affect the results and comparisons. The new ethanol-free (emollient) foam does not appear to produce greater penetration compared to the previous foam formulation in this model.

#### 2.6.4.4 Distribution

Upon absorption, topical corticosteroids are processed through pharmacokinetic pathways similar to systemically administered corticosteroids. Circulating levels of corticosteroids are typically well below the level of detection; however, the sponsor has conducted a clinical study in which blood clobetasol levels were measured.

#### **2.6.4.5 Metabolism**

Clobetasol propionate is primarily metabolized in the liver.

#### **2.6.4.6 Excretion**

Clobetasol propionate is excreted by the kidneys and in the bile.

#### **2.6.4.7 Pharmacokinetic drug interactions**

No new data or information on pharmacokinetic drug interactions were submitted.

#### **2.6.4.8 Other Pharmacokinetic Studies**

No new nonclinical pharmacokinetic studies on clobetasol propionate have been conducted.

#### **2.6.4.9 Discussion and Conclusions**

Nonclinical studies have shown that clobetasol propionate is absorbed through animal and human skin. The penetration of clobetasol propionate through human skin in the in vitro model was not greater for the new ethanol-free foam compared to the existing Olux<sup>®</sup> foam. If systemic absorption in humans follows this same trend, then the new foam may not produce any greater systemic effects than the previously approved Olux<sup>®</sup> foam. Clearance of clobetasol propionate is mainly by the liver, bile and feces.

#### **2.6.4.10 Tables and figures to include comparative TK summary**

No new nonclinical pharmacokinetic studies on clobetasol propionate have been conducted.

### **2.6.5 PHARMACOKINETICS TABULATED SUMMARY**

No new nonclinical pharmacokinetic studies on Primolux<sup>™</sup> have been conducted. See summaries above.

### **2.6.6 TOXICOLOGY**

#### **2.6.6.1 Overall toxicology summary**

General toxicology: Please see the reviews associated with IND 67,818 and NDA 19-323.

Genetic toxicology: Under the tested conditions, clobetasol propionate and sorbitan monolaurate were non-mutagenic in the bacterial reverse mutation assay. Clobetasol propionate elicited a positive response at 24 hours but not at 48 hours in the mouse micronucleus assay at 2000 mg/kg. Sorbitan monolaurate was negative in the mouse micronucleus assay at doses up to 2000 mg/kg. Under the tested conditions, clobetasol

propionate and sorbitan monolaurate were non-mutagenic in the L5178Y TK+/- mouse lymphoma mutagenesis assay.

Carcinogenicity: The sponsor has committed to conduct dermal carcinogenicity and photocarcinogenicity studies during Phase 4. See timelines below.

Reproductive toxicology: Clobetasol, like other corticosteroids, is teratogenic in animals even when administered at relatively low doses. Reproductive toxicity studies with clobetasol have been previously conducted by Glaxo SmithKline and others. The results of these studies have been reviewed in the NDAs submitted by Glaxo SmithKline for their clobetasol products.

Local tolerance: Primolux™ is essentially non-irritating on rabbit skin.

Special toxicology: Primolux™ is a slight irritant in rabbit eyes.

#### **2.6.6.2 Single-dose toxicity**

Please see the reviews associated with NDA 19-323. No new toxicity studies on clobetasol propionate have been submitted.

#### **2.6.6.3 Repeat-dose toxicity**

Please see the reviews associated with NDA 19-323. No new toxicity studies on clobetasol propionate have been submitted.

#### **2.6.6.4 Genetic toxicology**

**Study title**: Clobetasol Propionate: Bacterial Reverse Mutation Test: Plate Incorporation and Preincubation Method for Solids

**Key findings**: Under the tested conditions, clobetasol propionate was non-mutagenic in the bacterial reverse mutation assay.

**Study no.:** 04-04-003A

**Volume #, and page #:** Module 4, 423311, electronic

**Conducting laboratory and location**

**Date of study initiation:** May 5, 2004

**GLP compliance:** Yes

**QA reports:** yes ( X ) no ( )

**Drug, lot #, and % purity:** Not specified

#### **Methods**

Strains/species/cell line: *Salmonella typhimurium* strains TA97a, TA98, TA100 and TA1535; *Escherichia coli* strain WP2 *uvrA*

Doses used in definitive study: 10, 50, 100, 500, 1000 and 2500 µg/plate

Basis of dose selection: Preliminary plate incorporation assay

Negative controls: DMSO

Positive controls: 2-nitrofluorene (25 µg/plate), sodium azide (2 µg/plate), 2-aminoanthracene (2.5-25 µg/plate), ENNG (2 µg/plate), DMBA (20 µg/plate) and ICR 191 Acridine mutagen (2 µg/plate)

Incubation and sampling times: Plates were incubated for 48-68 hours.

## Results

Study validity: Revertant colonies were counted by hand, unless excessive toxicity or precipitate was present. Tests were conducted in triplicate. Mean positive control values must have been at least two fold higher than the concurrent negative control for each tester strain and condition. The mean number of revertants observed in the negative controls was within historical control ranges. A response was considered positive if the average number of revertants in any strain at any concentration were at least two times greater than the average number of revertants in the concurrent vehicle control and/or if there is a concentration-related increase in the mean revertants per plate in the same strain. A response was considered negative if there were no test article concentrations with an average number of revertants that were at least two times greater than the average number of revertants in the concurrent vehicle control and there were no positive concentration-related increases in the mean revertants per plate in the same strain. This study appears to be valid.

Study outcome: No increase in revertant frequency in any strain at any concentration with or without metabolic activation was observed. Toxicity was noted at high concentrations in strains TA97a, TA100, TA1535 and WP2 *uvrA*.

**Study title:** Sorbitan Monolaurate: Bacterial Reverse Mutation Test: Plate Incorporation and Preincubation Method for Liquids

**Key findings:** Under the tested conditions, sorbitan monolaurate was non-mutagenic in the bacterial reverse mutation assay.

**Study no.:** 04-04-002A

**Volume #, and page #:** Module 4, 423313, electronic

**Conducting laboratory and location:** ~~\_\_\_\_\_~~

**Date of study initiation:** May 5, 2004

**GLP compliance:** Yes

**QA reports:** yes ( X ) no ( )

**Drug, lot #, and % purity:** Not specified

## Methods

Strains/species/cell line: *Salmonella typhimurium* strains TA97a, TA98, TA100 and TA1535; *Escherichia coli* strain WP2 uvrA

Doses used in definitive study: 10, 50, 100, 500 and 1000 µg/plate

Basis of dose selection: Preliminary plate incorporation assay

Negative controls: DMSO

Positive controls: 2-nitrofluorene (25 µg/plate), sodium azide (2 µg/plate), 2-aminoanthracene (2.5-25 µg/plate), ENNG (2 µg/plate), DMBA (20 µg/plate) and ICR 191 Acridine mutagen (1-2 µg/plate)

Incubation and sampling times: Plates were incubated for 48 hours.

## Results

Study validity: Revertant colonies were counted by hand. Tests were conducted in triplicate. Mean positive control values must have been at least two fold higher than the concurrent negative control for each tester strain and condition. The mean number of revertants observed in the negative controls was within historical control ranges. A response was considered positive if the average number of revertants in any strain at any concentration were at least two times greater than the average number of revertants in the concurrent vehicle control and/or if there is a concentration-related increase in the mean revertants per plate in the same strain. A response was considered negative if there were no test article concentrations with an average number of revertants that were at least two times greater than the average number of revertants in the concurrent vehicle control and there were no positive concentration-related increases in the mean revertants per plate in the same strain. This study appears to be valid.

Study outcome: No increase in revertant frequency in any strain at any concentration with or without metabolic activation was observed. Toxicity was noted at high concentrations in strains TA97a, TA100 and TA98.

**Study title:** Clobetasol Propionate: *In vivo* Micronucleus in Mouse Bone Marrow for Solids: Single Administration

**Key findings:** Clobetasol propionate is positive in the mouse micronucleus assay at a dose of 2000 mg/kg.

Study no.: 04-04-003MN

Volume #, and page #: 1, Supplement 1

Conducting laboratory and location: \_\_\_\_\_

Date of study initiation: October 1, 2004

GLP compliance: Yes

QA reports: yes ( X ) no ( )

Drug, batch #, and % purity: clobetasol propionate, 7135/M1, 99.6%

### Methods

Strains/species/cell line: CD-1® (ICR) BR mice

Doses used in definitive study: 800, 1400 and 2000 mg/kg clobetasol propionate;

Basis of dose selection: preliminary study

Negative controls: vehicle (corn oil)

Positive controls: 70 mg/kg cyclophosphamide

Incubation and sampling times: 24 or 48 hours

### Results

Study validity: At least five animals/sex were assigned to each dose and time group. Animals were exposed via oral gavage in a single dose of corn oil vehicle. Vehicle and HD animals were sacrificed at 24 or 48 hours. LD, MD and positive control animals were sacrificed at 24 hours. Animals were monitored once between 1 and 6 hours post dose and daily thereafter. Three slides per animal were prepared, fixed in methanol and stained with Giemsa. Slides were scored microscopically by someone other than the technician that prepared the slides. At least 2000 PCEs per animal were scored for the presence of micronuclei. The test article was considered positive if a dose-related increase in the number of MN-PCEs or a clear increase in the number of MN-PCEs in a single dose group at a single sampling time was observed.

Study outcome: No adverse clinical observations were noted. The 48-hour HD groups had somewhat decreased PCE fractions, indicating mild bone marrow toxicity. The positive control caused clear increases in MN-PCEs in both sexes, without causing excessive toxicity. MN-PCEs were increased in the 24-hour male HD animals. In HD females, a slight increase was noted at 24 hours, but it was not statistically significant.

Clobetasol propionate, at 2000 mg/kg, produced a positive response at 24 hours in the *in vivo* mouse micronucleus assay. At 48 hours, a positive response was not seen in these mice. It is unlikely that similar doses could be achieved clinically with a topical



**Study outcome:** One male mouse from the LD and HD groups had a red perioral substance. No indications of toxicity were observed. The positive control elicited clear increases in MN-PCEs in both sexes, without causing excessive toxicity. Numbers of MN-PCEs were not increased in any sorbitan monolaurate group as compared to the corresponding negative controls.

**Study title:** Clobetasol Propionate: L5178Y TK+/- Mouse Lymphoma Assay for Solids

**Key findings:** Under the tested conditions, clobetasol propionate was non-mutagenic in the L5178Y TK+/- mouse lymphoma mutagenesis assay.

**Study no.:** 04-04-003MLA

**Volume #, and page #:** Module 4, 423312, electronic

**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** May 24, 2004

**GLP compliance:** Yes

**QA reports:** yes ( X ) no ( )

**Drug, lot #, and % purity:** Not specified

## Methods

**Strains/species/cell line:** L5178Y TK+/- mouse lymphoma cells

**Doses used in definitive study:** 0.1, 0.2, 0.5, 1, 2, 5, 10 and 20 µg/mL

**Basis of dose selection:** Preliminary study

**Negative controls:** DMSO

**Positive controls:** cyclophosphamide monohydrate, methylmethanesulfonate and 4-Nitroquinoline N-oxide

**Incubation and sampling times:** Plates were incubated for 72-96 hours.

## Results

**Study validity:** Tests were done in duplicate. Results for the positive control were acceptable if at least one of the positive control-treated cultures had a mutant frequency that was three times or greater than the average MF of its solvent control cultures. A response was considered negative if there were no test article concentrations with a mutant frequency at least two times greater than the mutant frequency in the concurrent vehicle control and there was not a concentration-related or reproducible increase in mutant frequency. A response was considered positive if the mutant frequency at any test article concentration with 10% or greater growth was at least two times greater than the mutant frequency in the concurrent vehicle control and there was a concentration-related

or reproducible increase in mutant frequency. Results for the positive control were acceptable if they met the criteria for a positive response. This study appears to be valid.

Study outcome: Clobetasol propionate did not produce a significant increase in the total mutant frequency above negative control levels with or without metabolic activation.

**Study title:** Sorbitan Monolaurate: L5178Y TK+/- Mouse Lymphoma Assay for Liquids

**Key findings:** Under the tested conditions, sorbitan monolaurate was non-mutagenic in the L5178Y TK+/- mouse lymphoma mutagenesis assay.

**Study no.:** 04-04-002MLA

**Volume #, and page #:** Module 4, 423314, electronic

**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** May 24, 2004

**GLP compliance:** Yes

**QA reports:** yes ( X ) no ( )

**Drug, lot #, and % purity:** Not specified

## Methods

Strains/species/cell line: L5178Y TK+/- mouse lymphoma cells

Doses used in definitive study: 2.5, 5, 10, 20, 50, 100, 200 and 500 µg/mL

Basis of dose selection: Preliminary study

Negative controls: DMSO

Positive controls: cyclophosphamide monohydrate and methylmethanesulfonate

Incubation and sampling times: Plates were incubated for 72-96 hours.

## Results

Study validity: Tests were done in duplicate. Results for the positive control were acceptable if at least one of the positive control-treated cultures had a MF that was three times or greater than the average MF of its solvent control cultures. A response was considered negative if there were no test article concentrations with a mutant frequency at least two times greater than the mutant frequency in the concurrent vehicle control and there was not a concentration-related or reproducible increase in mutant frequency. A response was considered positive if the mutant frequency at any test article concentration with 10% or greater growth was at least two times greater than the mutant frequency in the concurrent vehicle control and there was a concentration-related or reproducible

increase in mutant frequency. Results for the positive control were acceptable if they met the criteria for a positive response. This study appears to be valid.

Study outcome: Sorbitan monolaurate did not produce a significant increase in the total mutant frequency above negative control levels with or without metabolic activation.

#### 2.6.6.5 Carcinogenicity

The sponsor has committed to conduct dermal carcinogenicity and photocarcinogenicity studies during Phase 4 according to the following timeline commitment submitted by the sponsor. These dates assume NDA approval on the PDUFA date of January 17, 2007.

##### Dermal Carcinogenicity Assay:

Study Protocol Submission:	Within 24 months of approval (January 17, 2009)
Study Initiation:	Within 32 months of approval (September 17, 2009)
Final Study Report Submission:	Within 42 months of study initiation (March 17, 2013)

##### Photocarcinogenicity Study:

Study Protocol Submission:	Within 24 months of approval (January 17, 2009)
Study Initiation:	Within 32 months of approval (September 17, 2009)
Final Study Report Submission:	Within 30 months of study initiation (March 17, 2012)

#### 2.6.6.6 Reproductive and developmental toxicology

##### Reproductive and developmental toxicology summary:

Clobetasol is teratogenic in animals even when administered at relatively low doses. Subcutaneous administration of up to 50 µg/kg in rats resulted in an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose. Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested (≥0.03 mg/kg). These doses are approximately 1.4 and 0.04 times the human topical dose of Primolux™ foam, respectively. Abnormalities seen included cleft palate and skeletal abnormalities. In rabbits, clobetasol propionate was teratogenic at doses of 3 and 10 µg/kg. These doses are approximately 0.02 and 0.05 times the human topical dose of Primolux™ foam, respectively. Abnormalities seen included cleft palate, cranioschisis and other skeletal abnormalities.

#### 2.6.6.7 Local tolerance

**Study title:** A primary skin irritation study in rabbits with Olux-E aerosol foam

**Key study findings:** Relatively minor evidence of skin irritation was observed in the rabbit from application of the test material under occlusion for 24 hours and there was no difference between abraded and nonabraded sites.

**Study no:** 3600.18

**Volume #2, page #394**

**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** January 14, 2004

**GLP compliance:** Yes

**QA reports:** Yes

**Drug, lot # and % purity:** Olux-E aerosol foam, Batch No. TKD-1C, purity not specified

**Formulation/vehicle:** ethanol-free foam

**Methods:** ↑

**Observations and times:** The gauze patches were removed 24 hours after application and the test sites were evaluated for erythema and edema 1, 24, 48 and 72 hours and up to 14 days after application.

**Results:** Exposure to the test material produced very slight to well-defined erythema at all tests sites at 1 hour after patch removal. Very slight edema was observed in three of the nonabraded sites and three of the abraded sites at the 24 hours time point. This irritation decreased with time such that the irritation at the nonabraded sites was resolved in three animals by day 7, one more animal by day 10 and the remaining two animals by day 14. At the abraded sites the irritation resolved in one animal by day 1, one animal by day 3 and the remaining four animals by day 10.

#### 2.6.6.8 Special toxicology studies

**Study title:** A primary eye irritation study in rabbits with Olux-E aerosol foam

**Key study findings:** The foam was considered to be a slight irritant in rabbit eyes.

**Study no:** 3600.17

**Volume #2, page #366**

**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** January 14, 2004

**GLP compliance:** Yes

**QA reports:** Yes

**Drug, lot # and % purity:** Olux-E aerosol foam, Batch No. TKD-1C, purity not specified

**Formulation/vehicle:** ethanol-free foam

**Methods:**

**Observations and times:** The eyes were examined for signs of irritation 1, 24, 48 and 72 hours after drug administration.

**Results:** Exposure to the test material produced conjunctivitis in all three animals at 1 hour after drug administration. No signs of irritation were observed at any later time point in any animal. No effects on the cornea or iris were noted.

**2.6.6.9 Discussion and Conclusions**

Connetics is relying on the Agency's previous findings of nonclinical safety for the reference listed drug (RLD), Temovate<sup>®</sup> Ointment, NDA 19-323, and supporting literature. In addition, Connetics conducted eight nonclinical studies to support this NDA. The sponsor has committed to conduct a dermal carcinogenicity and a photocarcinogenicity study as post-marketing commitments.

Clobetasol propionate and sorbitan monolaurate were non-mutagenic in the bacterial reverse mutation assay and the L5178Y TK+/- mouse lymphoma mutagenesis assay. Clobetasol propionate elicited a positive response at 24 hours but not at 48 hours in the mouse micronucleus assay at 2000 mg/kg. Sorbitan monolaurate was negative in the mouse micronucleus assay at doses up to 2000 mg/kg.

Clobetasol, like other corticosteroids, is teratogenic in animals even when administered at relatively low doses. Primolux<sup>™</sup> was found to be essentially non-irritating on rabbit skin; however, it was slightly irritating to rabbit eyes.

**2.6.6.10 Tables and Figures**

Please see the reviews associated with NDA 19-323. No new general toxicology studies on clobetasol propionate have been submitted.

**2.6.7 TOXICOLOGY TABULATED SUMMARY**

No new general toxicology studies on clobetasol propionate have been submitted. See summaries above.

**OVERALL CONCLUSIONS AND RECOMMENDATIONS**

**Conclusions:** There are no nonclinical safety issues relevant to the clinical use of Primolux™. This is a 505 (b) 2 application in which the sponsor is relying on the Agency's previous findings of nonclinical safety for the reference listed drug, Temovate® ointment. The sponsor conducted a clinical bridging study, a pharmacokinetic study comparing the bioavailability of Primolux™ Foam to that of Temovate® ointment.

**Unresolved toxicology issues:** The sponsor has committed to conduct dermal carcinogenicity and photocarcinogenicity studies with Primolux™ during Phase 4.

**Recommendations:** NDA 22-013 is approvable in regard to pharmacologic and toxicologic concerns.

**Suggested labeling:** The labeling for Primolux™ foam with regard to nonclinical safety will be the same as that approved for Olux® foam. The label is acceptable to this reviewer. The suggested changes described on page 3 of this review are shown below. The changes in the genetic toxicity paragraph are suggested to reflect the studies contained in this submission and the Temovate® ointment label. All other changes are recommended to include similar values and language as the label for Olux® foam.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Clobetasol propionate was non-mutagenic in four different test systems: the Ames test, the mouse lymphoma test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test. In the *in vivo* mouse micronucleus test a positive finding was observed at 24 hours, but not at 48 hours, following oral administration at a dose of 2000 mg/kg.

Studies in the rat following subcutaneous administration of clobetasol propionate at dosage levels up to 0.05 mg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

**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 to laboratory animals.

Clobetasol propionate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and when administered subcutaneously, it was a significant teratogen in both the rabbit and the mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human

topical dose of \_\_\_\_\_ Foam based on body surface area comparisons. Abnormalities seen included cleft palate and skeletal abnormalities.

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There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. \_\_\_\_\_ Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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