CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 209483
Supporting document/s:	SDN 1, 4
Applicant's letter date:	1-30-2017, 3-31-2017
CDER stamp date:	1-30-2017, 3-31-2017
Product:	Clobetasol Propionate Cream, 0.025%
Indication:	Plaque psoriasis
Applicant:	Promius Pharma, LLC
Review Division:	DDDP
Reviewer:	Jill C Merrill, PhD
Supervisor/Team Leader:	Barbara A Hill, PhD
Division Director:	Kendall Marcus, MD
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Promius Pharma, Inc. (Promius) intends to file a 505(b)(1) NDA for Clobetasol Propionate Cream, 0.025%. They have obtained the right of reference from Fougera Pharmaceuticals, Inc., for all forms of Temovate products (clobetasol propionate, 0.05%) included in NDAs 19322, 19323, 19966, 20337, and 20340. The intent of the lower concentration product (0.025%) in the current NDA is to maintain the efficacy seen at the higher concentration (0.05%) while potentially reducing the incidence of adverse hypothalamic-pituitary-adrenal (HPA) axis suppression.

1.2 Brief Discussion of Nonclinical Findings

Promius has obtained the right of reference from Fougera Pharmaceuticals Inc for all of the Temovate topical formulations. Therefore, Promius is relying on the data available for Temovate NDAs 19322, 19323, 19966, 20337 and 20340 to support the safety of their drug product. In addition, Promius has conducted repeat-dose dermal toxicity studies in rats up to 13 weeks (0.001, 0.005 and 0.025% BID; 0.004, 0.02, and 0.1 mg/kg/day) and in minipigs up to 4 weeks (0.005%, 0.025% and 0.05%; 0.1, 0.5 and 1.0 mg/kg/day), an acute dermal study in rabbits, an ocular irritation study using the bovine corneal opacity and permeability (BCOP) assay, a dermal photoirritation study in mice and a dermal sensitization study in guinea pigs. Considering the extent of immune suppression observed during the 13-week repeat-dose dermal toxicity study in rats, the Agency has waived the requirement for a two-year dermal carcinogenicity study in rats.

1.3 Recommendations

1.3.1 Approvability

Clobetasol Propionate Cream, 0.025% is approvable from a Pharmacology/Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

The sponsor's proposed label is basically a revision of the previously approved Temovate labels updated to be consistent with the Pregnancy, Lactation and Labeling Rule (PLLR). All the nonclinical information in Section 8 remains the same and is based on studies reviewed by the Division sufficiently long ago to make access to the original data highly unlikely. In a review of NDA 20340, Dr. Paul Brown stated that the data in earlier versions of the Temovate label have been corrected and the current version is consistent with his review. Thus the current review will be confined to updating the language to be consistent with other members of the same pharmacological class and the format as determined by PLLR. Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. The clinical reviewer will determine appropriate modifications to the clinical portions of Section 8 of the label. Except as where designated by PLLR format, it is recommended that the

underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the sponsor's label text. A clean copy of the revised labeling sections is provided in the Appendix.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

(b) (4) TRADENAME Cream is a corticosteri~~o~~id indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older. (1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary~~:~~

There are no (b) (4) available data on TRADENAME Cream in pregnant women to inform a drug-associated risk for adverse developmental outcomes. In animal reproduction studies, increased malformations, such as cleft palate and skeletal abnormalities, were observed after subcutaneous administration of clobetasol propionate to pregnant mice and rabbits. No comparisons of animal exposure with human exposure are provided due to minimal systemic exposure noted after topical administration of TRADENAME Cream *[see Clinical Pharmacology (12.3)]*.

(b) (4)

(b) (4)

Data

Animal Data~~:~~

[redacted] In an embryofetal development study in mice, subcutaneous administration of clobetasol propionate [redacted] resulted in fetotoxicity at the highest dose tested (1 mg/kg) and malformations at [redacted] the lowest dose [redacted] tested [redacted] (0.03 mg/kg). [redacted] Malformations seen included cleft palate and skeletal abnormalities. In an embryofetal development study in rabbits, subcutaneous administration of clobetasol propionate [redacted] resulted in malformations at doses of 0.003 and 0.01 mg/kg. [redacted] Malformations seen included cleft palate, cranioschisis, and other skeletal abnormalities.

[redacted]

Reviewer's comment: [redacted]

12 Clinical Pharmacology

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in corticosteroid responsive dermatoses is unknown. The contribution to efficacy by individual components of the vehicle has not been established.

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of [redacted] clobetasol propionate cream.

In a 13-week repeat dose toxicity study in rats, topical administration of [redacted] clobetasol [redacted] propionate [redacted] cream, 0.001, 0.005 and 0.025 % at corresponding doses of 0.004, 0.02 and 0.1 mg/kg/day resulted in corticosteroid class-related systemic effects such as reductions in body weight gain [redacted], reductions in total leukocytes and individual white cells, decrease in weight of adrenals, thymus, spleen, liver and lung. Histologically, there were decreased hematopoiesis in the bone marrow, thymic atrophy and mast cell infiltration of the mesenteric lymph nodes. All these effects were indicative of severe immune suppression consistent with long-term exposure to corticosteroids. A

no observable adverse effect level (NOAEL) was determined to be [redacted] clobetasol propionate cream, 0.001% (0.004 mg/kg/day) in male rats while a NOAEL could not be determined in females. The clinical relevance of the findings in animals to humans is not clear, but sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis.

Clobetasol propionate was not mutagenic in [redacted] three different test systems: the Ames test, [redacted] the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test. [redacted]

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

[redacted]

2 Drug Information

2.1 Drug

CAS Registry Number: 25122-46-7

Generic Name: Clobetasol propionate

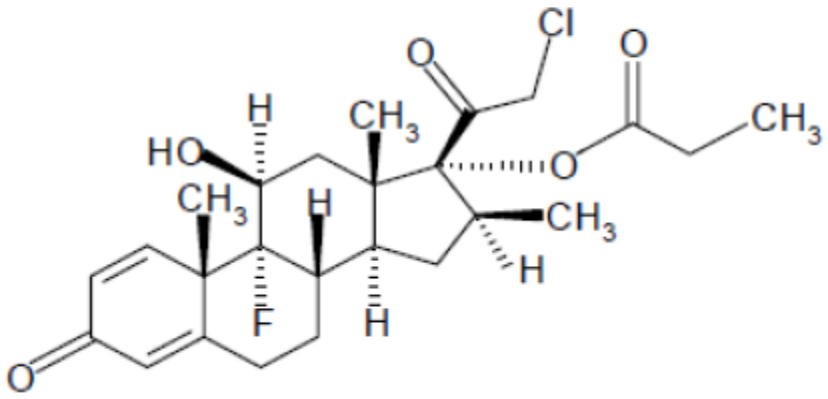
Code Name: DFD-06

Chemical Name: 21-chloro-9-fluoro-11β, 17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate

Molecular Formula/Molecular Weight: $C_{25}H_{32}ClFO_5$/ 467.0

Structure

3.2.S.1.2.1. Structural Formula



Pharmacologic Class: corticosteroid

2.2 Relevant INDs, NDAs, and MFs

IND 110799, clobetasol propionate cream, 0.025%, Promius Pharma, Inc.; submitted 3-30-2011

NDA 19322, Temovate® (clobetasol propionate) emulsion cream, 0.05%, Fougera Pharmaceuticals Inc.; approved 12-27-1985

NDA 19323, Temovate® (clobetasol propionate) ointment, 0.05%, Fougera Pharmaceuticals Inc.; approved 12-27-1985

NDA 19966, Temovate® (clobetasol propionate) solution, 0.05%, Fougera Pharmaceuticals Inc.; approved 2-22-1990

NDA 20337, Temovate® (clobetasol propionate) gel, 0.05%, Fougera Pharmaceuticals Inc.; approved 4-29-1994

NDA 20340, Temovate® E (clobetasol propionate) emulsion cream, 0.05%, Fougera Pharmaceuticals Inc.; approved 6-17-1994

(b) (4)

2.3 Drug Formulation

Table 3.2.P.1.2-1: Qualitative and Quantitative composition of DFD-06 (Clobetasol propionate Cream, 0.025%)

Ingredients	Reference / Standard	% w/w	Function
Clobetasol propionate	USP	0.025	Active
Cetostearyl alcohol	NF	(b) (4)	
Glyceryl stearate & PEG 100 stearate	IH*		
White wax	NF		
Diethylene glycol monoethyl ether	NF		
Butylated hydroxytoluene	NF		
Isopropyl myristate	NF		
Cyclomethicone	NF		
Methylparaben	NF		
Propylparaben	NF		
Purified water Q.S.	USP		
		(b) (4)	

2.4 Comments on Novel Excipients

Not applicable.

2.5 Comments on Impurities/Degradants of Concern

Not applicable.

2.6 Proposed Clinical Population and Dosing Regimen

Apply a thin layer of clobetasol propionate cream, 0.025% to the affected skin areas twice daily and rub in gently and completely. Wash hands after each application. Use clobetasol propionate cream, 0.025% for up to 2 consecutive weeks of treatment.

2.7 Regulatory Background

There was no pre-IND meeting for IND 110799. The original IND was submitted on March 30, 2011 with the intent to follow a 505(b)(2) regulatory pathway with Temovate® E (clobetasol propionate emollient cream), 0.05% as the listed drug. The sponsor requested inactivation of this IND on July 31, 2012. The IND was reactivated on July 3, 2013. During a pre-NDA meeting (October 12, 2016), Promius informed the Agency of their intent to pursue a 505(b)(1) regulatory pathway. Promius has obtained a right of

reference from Fougera Pharmaceuticals Inc. for all forms of Temovate products (clobetasol propionate 0.05%) included in NDAs 19322, 19323, 19966, 20337, and 20340 and will rely on the data available in these NDAs for the systemic nonclinical safety data of clobetasol propionate.

3 Studies Submitted

3.1 Studies Reviewed

General Toxicology
DFD-06: 10-Day dermal toxicity and toxicokinetic study in minipigs with 0.025% w/w Clobetasol Propionate (8286593)

DFD-06: A 28-day dermal toxicity and toxicokinetic study in minipigs with Clobetasol Propionate Cream (8286594)

Special Toxicology
Acute dermal irritation/corrosion study in rabbits (OECD) with Clobetasol Propionate Cream 0.025% w/w (MB-13-21810.03)

Delayed contact dermal sensitization test in guinea pigs – Buehler Method – with Clobetasol Propionate Cream 0.025% w/w (MB 13-21810.06)

Dermal phototoxicity screening test in mice (MB 13-21810.50)

Bovine corneal opacity and permeability test (BCOP) with clobetasol propionate cream 0.025% w/w (MB 13-21810.09)

3.2 Studies Not Reviewed

Pharmacokinetics

Bioanalytical method validation for the estimation of clobetasol propionate in rat plasma by LC-MS/MS (139/PK/002)

Validation of a method for the determination of clobetasol propionate in rat plasma (K_2EDTA) by liquid chromatography-tandem mass spectrometry (LC-MS/MS; 1401166)

Validation of a method for the determination of clobetasol propionate in minipig plasma by HPLC with MS/MS detection (8322327)

The following studies have been previously reviewed under the original IND. Summaries are provided in the corresponding section of this document.

Toxicology

A 13-week study of clobetasol propionate cream (DFD-06) by dermal administration in rats with a 4-week recovery period (20085039)

Clobetasol Propionate Cream 0.025% w/w: 4-week dermal toxicity study in Wistar rats (SE/36/01)

3.3 Previous Reviews Referenced

IND 110799 Pharmacology/Toxicology reviews

4 Pharmacology

4.1 Primary Pharmacology

Like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipuritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

4.2 Secondary Pharmacology

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

4.3 Safety Pharmacology

The literature and previous clinical experience with Temovate drug products suggest there are no safety pharmacology concerns associated with clobetasol propionate (0.05%) following dermal administration limited to <50 g/week. Thus treatment with clobetasol propionate cream (0.025%) as prescribed does not pose a safety pharmacology concern.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Refer to the Clinical Pharmacology review for a summary of the clinical pharmacokinetics information available for clobetasol propionate cream, 0.025%.

5.2 Toxicokinetics

(see Section 6.2 – Dermal toxicity study in minipigs)

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were included in the NDA submission.

6.2 Repeat-Dose Toxicity

Clobetasol Propionate Cream 0.025% w/w: 4-week dermal toxicity study in Wistar rats

In a 4-week dermal toxicity study in rats conducted with clobetasol propionate cream (0.025%) significant immunosuppression was observed when tested at a dose level of 0.1 mg clobetasol/kg/day (SE/36/01). (b) (4)

Reviewer's comment: (b) (4)

(b) (4)

13-week dermal dose range-finding study in rats

Clobetasol propionate cream at concentrations of 0 (saline control), 0 (vehicle control), 0.001, 0.005, and 0.025% was applied twice daily to ~10% total body surface area to Sprague Dawley rats (n=10/sex/group) for 13 weeks (20085039) in a dose range-finding study for an eventual 2-year dermal carcinogenicity study. These concentrations corresponded to daily doses of 0, 0, 0.004, 0.02, or 0.1 mg/kg/day, respectively. Test article-related effects attributed to the immunosuppressive properties of corticosteroids were observed in all treated animals and included lower body weights at concentrations ≥0.005% in males and at all concentrations in females; reductions in total leukocytes at ≥0.005% in both sexes; decrease in weight of adrenals (at all dose levels in both sexes), thymus (at ≥0.005% in both sexes), spleen (at 0.025% in males and at ≥0.005% in females), liver and lung of females at 0.025%; thymic atrophy in both sexes at 0.025% and decreased hematopoiesis in the bone marrow in females at 0.025%. The NOAEL for dermal administration of clobetasol propionate cream for 13 weeks was 0.001% (0.004 mg/kg/day) for males; a NOAEL for females could not be determined.

Reviewer's comment: Based on the severe immune suppression seen during the 13-week study, the sponsor's waiver request was granted for the conduct of a 2-year dermal carcinogenicity study.

Study title: A 28-day dermal toxicity and toxicokinetic study in minipigs with Clobetasol Propionate Cream

Study no.:	8286594
Study report location:	electronic
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10-22-2015
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	Clobetasol propionate cream 0.005% w/w, DERCT-230/09-15, 102.7% Clobetasol propionate cream 0.025% w/w, GMS-1C, 101.1% Clobetasol propionate cream 0.05% w/w, DERCT-232/09-15, 100.9% Vehicle of Clobetasol Propionate Cream, DERCT-227/07-15, complies 0.9% sodium chloride injection, USP, C982553, pass

Key Study Findings

In minipigs, daily dermal administration of clobetasol propionate cream at concentrations up to 0.05% (1.0 mg/kg/day clobetasol propionate) for 28 days resulted in test article-related changes in body weight, clinical pathology, histopathology and organ weights. Based on lower adrenal weights in both males and females treated with the lowest dose tested (0.1 mg/kg as 0.005% cream), a NOAEL could not be determined in this study. These findings are consistent with topical exposure to corticosteroids.

Methods

Doses:	0 (untreated control), 0 (vehicle control), 0.005%, 0.025%, 0.05% clobetasol propionate cream (0, 0, 0.1, 0.5, 1.0 mg/kg/day)*
Frequency of dosing:	Once daily
Route of administration:	Applied to clipped dorsal skin (10% body surface area) without occlusion. Technical staff remained with the animal until the formulation dried.
Dose volume:	2 g/kg
Formulation:	Clinical formulation
Species/Strain:	Minipig/Gottingen
Number/Sex/Group:	4
Age:	4-5 months
Weight:	Males: 8.6 – 12 kg; females: 9.5 – 11.9 kg
Satellite groups:	none
Unique study design:	none
Deviation from study protocol:	None significant to integrity of test results

*Doses were selected based on findings of a 10-day range-finding dermal toxicity study conducted in minipigs (8286593). In the 10-day study clobetasol propionate cream, 0.025%, at a dose of 0.5 mg/kg/day (0.25 mg/kg/dose, *b.i.d.*) did not cause local or systemic toxicity. Clobetasol propionate cream, 0.05% is the maximum feasible concentration. The maximum feasible dose (0.05% x 2 g/kg =1 mg/kg/day) was chosen as the high dose and is anticipated to cause some local and/or systemic toxicity. The lower doses were selected to study the dose response. Clobetasol propionate cream, 0.025%, which is the intended clinical formulation, was used for the mid-dose group.

Observations and Results

Mortality

Animals were checked twice daily for mortality, abnormalities and signs of pain or distress. All animals survived to scheduled necropsy.

Clinical Signs

Cageside observations were conducted once daily during predose and dosing phases. Detailed observations were conducted 3 times during the predose phase and weekly during the dosing phase. No clinical observations were attributed to administration of test article.

Dermal signs

Dermal irritation was evaluated on each animal's dosing site once during the predose phase and daily 1 hour following completion of exposure period during the dosing phase. Application site was scored/graded using a modified Draize technique.

No test article-related dermal changes were noted (see Text Table 4.2). Dermal changes were limited to a low incidence of edema and erythema, noted most frequently in vehicle control animals.

Text Table 4.2: Incidence and Frequency of Edema and Erythema during the Dosing Phase

	Group	1: (Sham Control)	2: (Vehicle Control)	3: 0.1 mg/kg/day	4: 0.5 mg/kg/day	5: 1.0 mg/kg/day
Number of animals/sex/group		4	4	4	4	4
Very slight edema	Male	0 (0)	12 (2)	3 (1)	0 (0)	1 (1)
	Female	0 (0)	13 (1)	0 (0)	3 (1)	0 (0)
Slight edema	Male	0 (0)	0 (0)	8 (1)	0 (0)	0 (0)
	Female	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Very slight erythema	Male	0 (0)	6 (2)	8 (1)	0 (0)	2 (1)
	Female	0 (0)	21 (2)	0 (0)	3 (1)	1 (1)
Well-defined erythema	Male	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Female	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)

Note: Values represent the total number of observations (number of animals affected) during 29 days of observation for each animal

Body Weights

Body weights were recorded 3 times during the predose phase, and weekly during the dosing phase. Mean body weights relative to the vehicle controls were 8 and 17% less for males given 0.025% and 0.05% (0.5 and 1.0 mg/kg/day) and 10, 18, and 20% less for females given 0.005%, 0.025% or 0.05% (0.1, 0.5, or 1.0 mg/kg/day), respectively. This is a known effect of corticosteroids.

Feed Consumption

Qualitative feed consumption was recorded daily. The test article had no effect on feed consumption.

Ophthalmoscopy

Ophthalmic examinations were conducted once during the predose phase and on Day 23 of the dosing phase using an indirect ophthalmoscope. The eyes were dilated with a mydriatic agent prior to examination. No visible lesions were noted during ophthalmic examinations.

ECG

ECGs were recorded predose and once on Day 28 (~24 hours post the 6th dose during Week 4, but before the 7th dose) of the dosing phase. ECGs were recorded using 6 leads. Animals were anesthetized with midazolam and dexmedetomidine for each data collection.

On Day 28 of the dosing phase (24 hours post the 27th dose), mean heart rates were lower in animals given 0.025% or 0.05% (0.5 or 1.0 mg/kg/day) compared with mean heart rates of sham control or vehicle control animals. Heart rates were 51% or 52% lower in males given 0.05% (1.0 mg/kg/day) compared with sham or vehicle-treated

controls, respectively and 32% or 38% lower in females given 0.05% (1.0 mg/kg/day) compared with sham or vehicle-treated controls, respectively. The animals given 0.005% (0.1 mg/kg/day) showed no significant lowering of heart rate. The heart rate-corrected QT (QTc) interval was calculated using the Fridericia method and was found to be shortened in males given 0.025% or 0.05% (0.5 or 1.0 mg/kg/day), but not in females. The effect in QTc was considered secondary to the fall in heart rate. No other quantitative ECG changes were observed. No rhythm abnormalities or qualitative ECG changes were observed and no correlative clinical observations or pathologic findings were noted.

Reviewer's comment: As per ICH Guidance for Industry S7A Safety Pharmacology, it is preferable to use unanesthetized animals in conducting in vivo studies for human pharmaceuticals.

Hematology

Blood samples were collected during the predose period and prior to termination from the anterior vena cava from overnight fasted animals and analyzed for the following parameters: red blood cell (erythrocyte) count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, white blood cell (leukocyte) count, differential blood cell count, blood smear, reticulocyte count, prothrombin time, and activated partial thromboplastin time. Potassium EDTA and sodium citrate were the anticoagulants used for the hematology and coagulation parameters, respectively.

Test article-related changes in hematology were noted on day 29 of the dosing phase in animals administered ≥0.025% (0.5 mg/kg/day) and included the following:

- Moderate to markedly decreased absolute reticulocyte count (-49 to -84% control) in animals given ≥0.025% (0.5 mg/kg/day)
- Mild to moderately decreased absolute lymphocyte count (-22 to -63% control) in animals given ≥0.025% (0.5 mg/kg/day)
- Mildly decreased absolute eosinophil (-39 to -75% control) and basophil (-71% control) counts in females given ≥0.025% (0.5 mg/kg/day)
- Minimal to mildly increased absolute neutrophil count (+90 to +379% control) in animals given ≥0.025% (0.5 mg/kg/day)
- Mildly increased absolute monocyte count (+93% control) in females given ≥0.005% (0.1 mg/kg/day)

Decreased reticulocyte count was correlated microscopically with decreased bone marrow cellularity (sternum and femur). Decreased lymphocytes may have been related to the decreased thymic lymphocytes noted microscopically. Increased

neutrophil and monocyte counts and decreased lymphocyte, eosinophil, and basophil counts are frequently seen with glucocorticoid administration. No test article-related changes were observed in coagulation parameters.

Clinical Chemistry

Blood samples were collected during the predose period and prior to termination from the anterior vena cava from overnight fasted animals and analyzed for the following parameters: glucose, sorbitol dehydrogenase, urea nitrogen, creatinine, total protein, albumin, globulin, albumin:globulin ratio, cholesterol, triglycerides, total bilirubin, alkaline phosphatase, gamma glutamyltransferase, aspartate aminotransferase, calcium, inorganic phosphorus, sodium, potassium, chloride. Clinical chemistry samples were collected without anticoagulant.

A minimal increase in glucose (6.6 to 20% increase relative to control values) was seen in animals given ≥0.025% (0.5 mg/kg/day). This is considered a consequence of corticosteroid induced gluconeogenesis. Mildly decreased creatinine (17 to 33% decrease relative to control values) in males given ≥0.025% (0.5 mg/kg/day) is likely a consequence of decreased body weight and potential decrease in muscle mass. An increase in total protein (males only; 8.1 to 13% increase relative to control values), primarily due to increased globulin in animals given ≥0.005% (0.1 mg/kg/day) was suggestive of inflammation; however, evidence of inflammation was not observed microscopically. Increased urea nitrogen (25 to 117% relative to control values) may have reflected amino acid mobilization from protein breakdown during gluconeogenesis. Mildly increased cholesterol (31 to 63% relative to control values) was noted in animals given ≥0.025% (0.5 mg/kg/day) and a definitive mechanism is undetermined.

Urinalysis

Urine samples were collected during the overnight fasted period prior to blood collection during the predose period and prior to termination and analyzed for the following parameters: appearance (clarity and color), volume, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, microscopic examination of sediment. No test article-related effect was observed in urinalysis test results.

No test article-related changes were observed in urinalysis parameters.

Gross Pathology

On day 29 overnight fasted animals were anesthetized with an intramuscular dose of ketamine (10 mg/kg) and dexmedetomidine (0.02 mg/kg), then treated with sodium pentobarbital, exsanguinated and necropsied. Terminal body weights were recorded. An examination of the external features of the carcass was performed including all external body orifices, abdominal, thoracic and cranial cavities, organs and tissues. No test article-related gross findings were observed at necropsy.

Organ Weights

The following organs were weighed: adrenal, brain, cervix, epididymis, heart, kidney, liver, lungs with large bronchi, ovary, pituitary gland, prostate, spleen, testis, thymus, thyroid, uterus.

Lower mean adrenal weight parameters (absolute and relative to body and/or brain) were noted in animals given ≥0.005% (0.1 mg/kg/day) compared to the sham control and vehicle control groups (see Text Table 4.3, taken directly from the study report). Adrenal weight reduction was correlated microscopically with minimal to slight atrophy of the zona fasciculata in the adrenal cortex. Lower mean unadjusted thymic weights were noted in animals given 0.005% (0.1 mg/kg/day) compared to the vehicle control group. Lower mean thymus weight parameters (absolute and relative to body and/or brain) were noted in animals given ≥0.025% (0.5 mg/kg/day) and were correlated microscopically with decreased lymphocytes in the thymic cortex. Lower mean testis weight parameters (absolute and relative to body and/or brain) were noted in males given ≥0.025% (0.5 mg/kg/day) compared to the vehicle and sham control animals. These weight differences are considered related to the minimal to slight bilateral atrophy of interstitial/Leydig cells.

Text Table 4.3: Test Article-Related Changes in Organ Weight Parameters

	Clobetasol Propionate Cream									
Sex	Males					Females				
Dose Level (mg/kg/day)	0[a]	0[b]	0.1	0.5	1.0	0[a]	0[b]	0.1	0.5	1.0
Adrenal										
Absolute Weight (g)	1.689	-23[c]	-40[c]	-56[cd]	-56[cd]	1.502	-12	-31[c]	-45[cd]	-41[cd]
Body Weight Ratio (%)	0.0129	-23	-40[c]	-52[cd]	-46[c]	0.0107	-13	-24	-34	-28
Brain Weight Ratio (%)	2.9633	-23[c]	-45[cd]	-56[cd]	-54[cd]	2.7039	-19	-33[c]	-41[c]	-37[c]
Thymus										
Absolute Weight (g)	6.969	+11	-29[d]	-54[cd]	-45[cd]	6.963	+16[c]	-9[d]	-49[cd]	-61[cd]
Body Weight Ratio (%)	0.0528	+11	-27	-50[cd]	-33[d]	0.0497	+15	0	-39[cd]	-52[cd]
Brain Weight Ratio (%)	12.3373	+7	-34[d]	-53[cd]	-44[cd]	12.5020	+8	-12	-45[cd]	-58[cd]
Testis										
Absolute Weight (g)	46.864	-5	-4	-22	-27	NA	NA	NA	NA	NA
Body Weight Ratio (%)	0.3580	-5	-4	-14	-11	NA	NA	NA	NA	NA
Brain Weight Ratio (%)	82.2854	-6	-12	-20	-24	NA	NA	NA	NA	NA

a 0.9% Sodium Chloride Injection, USP (sterile saline).
b Placebo of Clobetasol Propionate Cream.
c Statistically significant (absolute or relative) compared with sham control article mean value.
d Statistically significant (absolute or relative) compared with vehicle control article (placebo) mean value.
Note: Values for absolute weight and ratio of organ weights (relative to body or brain) for vehicle control and dosed groups expressed as percentage difference from sham control mean value

Histopathology

The following tissues were preserved in 10% neutral-buffered formalin and examined from all groups: adrenal, aorta, brain, cecum, cervix, colon, duodenum, epididymis, esophagus, eye, femur with bone marrow (articular surface of the distal end), gall bladder (drained), heart, ileum, jejunum, kidney, lacrimal glands, lesions, liver, lungs with large bronchi, lymph node (mandibular, mesenteric), mammary gland (females), muscle (biceps femoris), optic nerve, ovary, pancreas, pituitary gland, prostate, rectum, salivary gland (mandibular), sciatic nerve, seminal vesicle, skin/subcutis (treated),

skin/subcutis (untreated, inguinal), skin/subcutis (untreated, dorsal), spinal cord (cervical, thoracic, lumbar), spleen, sternum with bone marrow, stomach, testis, thymus, thyroid, tongue, urinary bladder, uterus, vagina.

Adequate Battery- yes

Peer Review- not specified

Histological Findings
Minimal to slight atrophy of the zona fasciculata in the adrenal cortex was noted in animals given ≥0.005% (0.1 mg/kg/day), which was characterized by smaller and fewer zona fasciculata cells and correlated with lower adrenal weights. Atrophy of interstitial/Leydig cells in the testis was noted for animals treated with ≥0.025% (0.5 mg/kg/day). The Leydig cells were less prominent and had less eosinophilic cytoplasm than that of sham or vehicle treated animals. This change correlated with a trend to lower testis weights in animals treated with ≥0.025% (0.5 mg/kg/day).

Text Table 4.4: Incidence and Severity of Test Article-Related Microscopic Findings

	Clobetasol Propionate Cream									
Sex	Males					Females				
Dose Level (mg/kg/day)	0[a]	0[b]	0.1	0.5	1.0	0[a]	0[b]	0.1	0.5	1.0
Adrenal, Cortex										
Number Examined	4	4	4	4	4	4	4	4	4	4
Atrophy, zona fasciculata										
Minimal	0	0	1	2	1	0	0	0	1	1
Slight	0	0	0	2	3	0	0	0	3	3
Testis										
Number Examined	4	4	4	4	4	NA	NA	NA	NA	NA
Atrophy, bilateral, interstitial/Leydig cells										
Minimal	0	0	0	2	1	NA	NA	NA	NA	NA
Slight	0	0	0	0	3	NA	NA	NA	NA	NA
Thymus										
Number Examined	4	4	4	3	3	4	4	4	4	4
Depletion, lymphocytes, cortex										
Slight	0	0	0	1	0	0	0	0	0	0
Moderate	0	0	0	2	0	0	0	0	2	0
Marked	0	0	0	0	3	0	0	0	2	4
Marrow, Femur										
Number Examined	4	4	4	4	4	4	4	4	4	4
Cellularity, Decreased										
Minimal	0	0	0	2	2	0	0	0	1	2
Slight	0	0	0	2	2	0	0	0	1	2
Marrow, Sternum										
Number Examined	4	4	4	4	4	4	4	4	4	4
Cellularity, Decreased										
Minimal	0	0	0	3	2	0	0	0	2	4

NA = Not applicable.
a 0.9% Sodium Chloride Injection, USP (sterile saline).
b Placebo of Clobetasol Propionate Cream.

Toxicokinetics

Blood samples were collected from all animals on Days 1 and 24 predose and at ~ 1, 2, 4, 6, 10, and 24 hours postdose. All concentration values of clobetasol propionate in the sham and vehicle control groups on Day 1 were below the lower limit of quantitation (LLOQ: 0.0100 ng/mL) with the exception of one animal which had a concentration of 0.114 ng/mL at the 24 hour timepoint. On Day 24 measurable concentrations of clobetasol propionate were detected in 2 sham control females and 2 vehicle control females. These values generally ranged from 0.0101 to 0.0279 ng/mL, except for a single concentration of 0.111 ng/mL in a single animal. Plasma concentrations observed in control animals are not further explained and are assumed to be acquired ex vivo.

Exposure to clobetasol propionate generally increased with the increase in dose level from 0.005% to 0.05% (0.1 to 1.0 mg/kg/day) on Days 1 and 24 (see Summary Table below, taken directly from the study report). The increases in C_{max} were generally dose proportional on Day 1 and 24. AUC_{0-24} values were generally dose proportional from 0.025% to 0.05% (0.5 to 1.0 mg/kg/day) on Day 1 and from 0.005% to 0.05% (0.1 to 1.0 mg/kg/day) on Day 24. Sex differences in clobetasol propionate mean C_{max} and AUC_{0-24} values were less than 2-fold. Accumulation of clobetasol propionate was observed after multiple dosing in minipigs. Systemic exposure to clobetasol propionate following topical application was minimal.

Summary of the Mean Clobetasol Propionate Cmax and AUC0-24 in Minipig Plasma

Interval (Day)	Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)
1	3	0.1	M	0.0462	NC
			F	0.0350	NC
			MF	0.0406	NC
	4	0.5	M	0.256	2.42
			F	0.133	1.60
			MF	0.194	2.01
	5	1.0	M	0.482	4.73
			F	0.265	2.93
			MF	0.374	3.83
24	3	0.1	M	0.133	2.34
			F	0.193	2.83
			MF	0.163	2.59
	4	0.5	M	1.39	15.3
			F	1.25	18.9
			MF	1.32	17.1
	5	1.0	M	2.59	35.2
			F	2.01	28.0
			MF	2.30	31.6

NC Not calculated due to less than three quantifiable values.

Dosing Solution Analysis

The vehicle control and test article formulations were analyzed by the sponsor prior to release and results provided in certificates of analysis. These formulations were dosed as supplied.

7 Genetic Toxicology

The sponsor has obtained the right of reference to the genetic toxicology studies conducted to support all forms of Temovate products (clobetasol propionate 0.05%) included in NDAs 19322, 19323, 19966, 20337, and 20340. The following information appears in the Mutagenesis section of the label for Temovate® E (clobetasol propionate) cream, 0.05% (NDA 20340).

Clobetasol propionate was nonmutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

8 Carcinogenicity

Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Data from a repeat-dose dermal toxicity study in rats (2008503) showed that clobetasol propionate cream, 0.025% caused marked immune suppression after receiving only 13 weeks of daily dosing. The anticipated survivability and general health concerns preclude conduct of a 2-year dermal carcinogenicity study with this drug product. Accordingly, the sponsor was granted a waiver for the conduct of the 2-year dermal carcinogenicity study. The results of the 13-week dermal rat study are incorporated into Section 13.1 of the proposed clobetasol propionate cream, 0.025% label.

9 Reproductive and Developmental Toxicology

The sponsor has obtained the right of reference to the reproductive and developmental toxicology studies conducted to support all forms of Temovate products (clobetasol propionate 0.05%) included in NDAs 19322, 19323, 19966, 20337, and 20340. The following information is based on the corresponding sections of the label for Temovate® E (clobetasol propionate) cream, 0.05% (NDA 20340).

9.1 Fertility and Early Embryonic Development

Studies in the rat following subcutaneous administration at dosage levels up to 50 µg/kg/day revealed no significant effect on the males. The females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Reviewer's comment: As per Dr. Paul Brown's NDA 20340 review, previous versions of the label listed the dose of the drug and the route of administration that was used in the rat fertility study incorrectly. The correct dose is 50 µg/kg/day (0.05 mg/kg/day) and the route is subcutaneous administration.

9.2 Embryonic Fetal Development

In an embryofetal development study in mice, subcutaneous administration of clobetasol propionate resulted in fetotoxicity at the highest dose tested (1 mg/kg) and malformations at the lowest dose tested (0.03 mg/kg). Malformations seen included cleft palate and skeletal abnormalities. In an embryofetal development study in rabbits, subcutaneous administration of clobetasol propionate resulted in malformations at doses of 0.003 and 0.01 mg/kg. Malformations seen included cleft palate, cranioschisis, and other skeletal abnormalities. Based on low systemic exposure after topical administration of clobetasol propionate cream, 0.025%, it is not possible to develop multiples of exposure.

10 Special Toxicology Studies

Study Title- Acute dermal irritation/corrosion study in rabbits (OECD) with Clobetasol propionate Cream 0.025% w/w (MB-13-21810.03)

Clobetasol propionate cream, 0.025% w/w produced reversible “very slight erythema” that was barely perceptible and cleared by Day 7. Clobetasol propionate cream, 0.025% w/w is not corrosive to the skin of rabbits under the conditions of this test.

Study Title- Delayed contact dermal sensitization test in guinea pigs-Buehler Method-with Clobetasol Propionate Cream 0.025% w/w (MB 13-21810.06)

Clobetasol propionate cream, 0.025% (Batch No: DERCT-132/04-13) was tested for delayed contact hypersensitivity in Hartley Albino guinea pigs (Buehler Method). In the Buehler guinea pig model, contact dermal sensitivity is manifested as increased erythema. Group 1 guinea pigs (ten males and ten females) received three topical induction applications of clobetasol propionate cream, 0.025% once per week for 3 weeks, administered as a 6 hour occluded dermal application. Skin reactions of the animals were recorded 24 and 48 hours following patch removal. Group 2 guinea pigs (five males and five females) were not induced and subsequently served as the naïve control at challenge.

Two weeks after the third induction, animals in Groups 1 and 2 were challenged with clobetasol propionate cream at naïve sites. The skin reactions of animals in both groups were recorded at 24 and 48 hours following patch removal. Body weights were recorded pretest and at termination. All animals were observed once per day for mortality, toxicity and systemic observations.

There were no signs of systemic toxicity and all animals gained weight during the study. Clobetasol propionate cream, 0.025% is not a dermal sensitizer under conditions of this assay. The sensitivity of guinea pigs to a positive control, 85% α-hexylcinnamaldehyde, is confirmed in the laboratory once every six months.

Study Title- Dermal phototoxicity screening in mice (MB 13-21810.50)

Clobetasol propionate cream, 0.025% (Batch No: DERCT-132/04-13) was screened for phototoxic potential when coadministered with ultraviolet light from a solar simulator to healthy mice. Thirty-six female BALB/c albino mice were dosed dermally as follows:

Group #	Group Description	SSL*	# of Animals	Dose Amount
1	Test Article (Clobetasol Propionate Cream 0.025% w/w)	Yes	6	100 µl equivalent /site
2	Test Article with wash off (Clobetasol Propionate Cream 0.025% w/w with wash off)	Yes	6	100 µl equivalent /site
3	Vehicle Control (Placebo of Clobetasol Propionate Cream)	Yes	6	100 µl equivalent /site
4	Positive Control (1.0% 8-MOP in Acetone)	Yes	6	100 µl/site
5	Negative Control (untreated)	Yes	6	---
6	Test Article – Unirradiated (Clobetasol Propionate Cream 0.025% w/w)	No	6	100 µl equivalent /site

*Solar Simulated Light Irridiation (SSL)

Prior to solar simulator irradiation the treated site for animals in Group 2 only was gently washed using distilled water. Mice in Groups 1-5 were irradiated with the solar simulator for 58 minutes after a 45 minute topical application period of test article, vehicle, or positive control using a Honle SOL-500 solar simulator with an H-1 filter to cut off UVB and UVC exposure. The distance between the source and the mice was adjusted to give an average irradiance of 2.9 mW/cm^2 and the period of irradiation was adjusted to yield a total UVA dose of 10.09 J/cm^2. Group 6 received the test article only and was not irradiated. Skin reactions were evaluated predose and at 4 hours following irradiation and ~24, 48, and 72 hours postdose according to a numerical Draize score. Evaluation of a phototoxic effect was based on the incidence and severity of the reactions.

No biologically significant change in body weight was observed over the course of the study. Mean body weight loss was observed in each group, with average losses ranging from 0.80% (Group 3) to 3.69% (Groups 1 and 4).

Erythema and edema were absent among animals in Groups 1, 2, 3, 5, and 6, at 4 hours post irradiation or at 24, 48 and 72 hours post dose. Erythema and edema were absent 4 hours post irradiation for animals in Group 4 (positive control; 1% methoxypsoralen in acetone). By Day 2, erythema was absent to very slight and edema was absent to moderate. As of Day 3, erythema was absent and edema was slight to severe. On Day 4, irritation persisted; erythema remained and edema was slight to moderate.

There were no abnormal physical signs observed among animals in Groups 1, 2, 3, 5, and 6. Animals in Group 4 appeared normal on Days 1 and 2. Beginning on Day 3, abnormal physical signs included swelling of the forepaws, swelling of the nose/mouth area, unkempt appearance, lethargy and yellow ocular discharge. Neither clobetasol propionate cream, 0.025% or the vehicle is considered to be phototoxic under the conditions of this tests.

Study Title- Bovine corneal opacity and permeability assay (BCOP)

Study No.: MB 13-21810.09
Study Initiation Date: 06/14/2013
GLP Compliance: Yes
Testing Facility: (b) (4)

Test article: clobetasol propionate cream, 0.025% w/w

Methods:
A 750 µL aliquot of clobetasol propionate cream 0.025% was administered to 3 isolated corneas. Following a 10 min exposure the corneas were washed, opacity was measured and the corneas were incubated for another 2 hr before final opacity and sodium fluorescein permeability were determined. Ethanol (100%) was used as the positive control and Minimal Essential Medium was used as the negative control.

Study Validity: The assay met the acceptability criteria.

Results:
The in vitro irritancy score (IVIS) was calculated for the test item using the following formula:

IVIS = corrected opacity value + (15 x corrected OD_{490} value)

Data is taken directly from raw data in the study report.

IVIS = -0.67 + (15 x 0.0)
IVIS = -0.67

The mean corrected opacity value -0.67 and the corrected OD value is 0.0. The IVIS is -0.67. Based on the CDER decision criteria, clobetasol propionate cream 0.025% is not a severe ocular irritant.

TEST ARTICLE - Clobetasol Propionate Cream 0.025% w/w

INDIVIDUAL TEST VALUES

CORNEA #	Individual Pretest Opacity Scores	Individual Scores Immediately After Treatment	Individual 2-Hour Scores	O.D. at 490 nm (Permeability)
L1	1	3	0	0.007
L2	2	4	0	0.004
L3	1	3	0	0.010

NEGATIVE CONTROL – MEM

INDIVIDUAL AND MEAN CALCULATED VALUES

Cornea #	Individual Pretest Opacity Score	Individual Scores Immediately After Treatment	Individual Immediate Post-Treatment Corrected Opacity Score[1]	Individual 2-Hour Scores	Individual 2-Hour Corrected Opacity Score[1]	O.D. at 490 (Permeability)
C_3 (neg)	2	2	0	2	0	0.006
C_4 (neg)	1	0	-1	0	-1	0.010
C_5 (neg)	1	1	0	0	-1	0.006
					Mean of Individual Optical Density=	0.007
					2-Hour Corrected Mean Opacity Score=	-0.66

TEST ARTICLE - Clobetasol Propionate Cream 0.025% w/w

INDIVIDUAL AND MEAN CALCULATED VALUES

CORNEA #	Corrected Opacity Scores		Individual Corrected O.D.[2]
	Individual Immediate Post-Treatment Corrected Opacity Score[1]	Individual 2-Hour Corrected Opacity Score[1]	
L1	2	-1	0
L2	2	-2	-0.003
L3	2	-1	0.003
		Corrected Mean Optical Density[3] =	0
		2- Hour Corrected Mean Opacity Score[4] =	-0.67

[1]Individual Corrected Opacity Score = 10-Minute (immediately post-treatment) or 2-Hour opacity score minus pretest opacity score

[2]Individual Corrected Optical Density = Individual test article or positive control OD minus the mean OD for negative control group. No correction was made for the negative control group

[3]Corrected Mean Optical Density = Mean of the individual corrected optical density values for a given dose group

[4]2-Hour Corrected Mean Opacity Score = Mean of the individual 2-hour corrected opacity scores for a given dose group minus the mean opacity score for the negative control group

11 Integrated Summary and Safety Evaluation

Topical repeat-dose toxicity studies conducted using the clinical clobetasol propionate cream formulation (0.025%) and an enhanced cream formulation (0.05%) produced effects in rats and minipigs that were consistent with the known effects of corticosteroids. The drug substance has been previously tested for systemic toxicity, genetic toxicology and reproductive and developmental toxicology. The sponsor has a right of reference to these studies and they stand in support of the current drug product.

Immune suppression observed during 13 weeks repeat-dose dermal toxicity testing in rats precluded conduct of a two-year dermal carcinogenicity study in rats.

Clobetasol propionate cream, 0.025%, for the treatment of plaque psoriasis is approvable from a Pharmacology/Toxicology perspective.

12 Appendix/Attachments

Recommended Label

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

TRADENAME Cream is a corticosteroid indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older. (1)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on TRADENAME Cream in pregnant women to inform a drug-associated risk for adverse developmental outcomes. In animal reproduction studies, increased malformations, such as cleft palate and skeletal abnormalities, were observed after subcutaneous administration of clobetasol propionate to pregnant mice and rabbits. No comparisons of animal exposure with human exposure are provided due to minimal systemic exposure noted after topical administration of TRADENAME Cream *[see Clinical Pharmacology (12.3)]*.

Data

Animal Data

In an embryofetal development study in mice, subcutaneous administration of clobetasol propionate resulted in fetotoxicity at the highest dose tested (1 mg/kg) and malformations at the lowest dose tested (0.03 mg/kg). Malformations seen included cleft palate and skeletal abnormalities. In an embryofetal development study in rabbits, subcutaneous administration of clobetasol propionate resulted in malformations at doses of 0.003 and 0.01 mg/kg. Malformations seen included cleft palate, cranioschisis, and other skeletal abnormalities.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in corticosteroid responsive dermatoses is unknown. The contribution to efficacy by individual components of the vehicle has not been established.

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate cream.

In a 13-week repeat dose toxicity study in rats, topical administration of clobetasol propionate cream, 0.001, 0.005 and 0.025% at corresponding doses of 0.004, 0.02 and 0.1 mg/kg/day resulted in corticosteroid class-related systemic effects such as reductions in body weight gain, reductions in total leukocytes and individual white cells, decrease in weight of adrenals, thymus, spleen, liver and lung. Histologically, there were decreased hematopoiesis in the bone marrow, thymic atrophy and mast cell infiltration of the mesenteric lymph nodes. All these effects were indicative of severe immune suppression consistent with long-term exposure to corticosteroids. A no observable adverse effect level (NOAEL) was determined to be clobetasol propionate cream, 0.001% (0.004 mg/kg/day) in male rats while a NOAEL could not be determined in females. The clinical relevance of the findings in animals to humans is not clear, but sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis.

Clobetasol propionate was not mutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

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

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/s/

JILL C MERRILL
08/23/2017

BARBARA A HILL
08/23/2017