CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208183Orig1s000

PHARMACOLOGY REVIEW(S)

Memorandum to file

Date: 10-14-2015

To: NDA 208183
SDN: SDN 12
Date: 09-28-2015

From: Jill Merrill, PhD., Pharm/Tox Reviewer
Through: Barbara Hill, PhD., Pharm/Tox Supervisor

Drug: Halobetasol Propionate Lotion, 0.05%

Indication: plaque psoriasis in patients 18 years of age and older

Sponsor: Ferndale Laboratories

Background:
The sponsor has developed a novel lotion formulation of halobetasol propionate as a topical treatment for plaque psoriasis. This NDA is a 505(b)(1) NDA from a Pharmacology/Toxicology perspective because the sponsor has obtained right of reference to all the nonclinical studies conducted to support approval of Ultravate Cream (NDA 19967, Ranbaxy Laboratories, Inc., approved 12-27-1990) and Ultravate Ointment (NDA 19968, Ranbaxy Laboratories, Inc., approved 12-17-1990) and has conducted additional nonclinical studies to support the safety of their new halobetasol propionate formulation (0.05%).

Current submission:
In the current submission the sponsor has provided recalculated stability tables for the total impurities, including (b) (4) which is considered genotoxic based on structural alerts. After 18 months of storage, the maximum level of (b) (4) was (b) (4) % (lot# 13082A).

Discussion:
Based on the maximum dose recommended for this drug product (50 g/week) and using drug product stored for up to 18 months, the maximum dermal dose of leachable (b) (4).

Calculations
(b) (4)

The appropriate ICH guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (ICH M7, June 23, 2014), has developed a Threshold of Toxicological Concern (TTC) concept to define acceptable intakes for any unstudied chemical that is considered to pose a negligible risk of carcinogenicity. Using the TTC concept in

the assessment of acceptable limits of mutagenic impurities in drug products, a value of 1.5 µg/day corresponds to a theoretical 10^{-5} excess lifetime risk of cancer. Balanced by the drug's benefit to the patient, this level of excess lifetime cancer risk associated with drug use is considered justifiable. Although the potential daily dose of (b) (4) in the proposed halobetasol propionate drug product ((b) (4)) is (b) (4) than this threshold level, Pharmacology/Toxicology does not have concerns about this level of potential mutagenic impurity because the 1.5 µg/day threshold level was developed based on oral exposure to the drug product. The sponsor's halobetasol propionate drug product is a lotion (i.e., intended for dermal application). The systemic exposure to (b) (4) will be much less than the calculated dermal dose due to the low level of dermal absorption of halobetasol propionate after topical administration.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JILL C MERRILL
10/14/2015

BARBARA A HILL
10/14/2015

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 208183
Supporting document/s:	SDN 1, 9
Applicant's letter date:	12/23/2014, 06/29/2015
CDER stamp date:	01/08/2015, 06/29/2015
Product:	Ultravate (halobetasol propionate lotion), 0.05%
Indication:	Plaque psoriasis in patients 18 years of age and older
Applicant:	Ferndale Laboratories, Inc.
Review Division:	DDDP
Reviewer:	Jill Merrill, PhD
Supervisor/Team Leader:	Barbara Hill, PhD
Division Director:	Kendall Marcus, MD
Project Manager:	Cristina Attinello

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

The sponsor has developed a novel lotion formulation of halobetasol propionate (HBP) as a topical treatment for plaque psoriasis. The sponsor has obtained a letter of authorization for Ultravate Cream and Ultravate Ointment. Therefore, this NDA is a 505(b)(1) NDA from a Pharmacology/Toxicology perspective because the sponsor has obtained right of reference to all the nonclinical studies conducted to support approval of Ultravate Cream and Ultravate Ointment and has conducted additional nonclinical studies to support the safety of the new HBP lotion, 0.05% formulation. The active ingredient, HBP, is well characterized and the concentration (0.05%) is known to be safe and effective as an anti-inflammatory and antipuritic agent in different topical dosage forms. HBP is a super high potency corticosteroid, known to cause hypothalamic-pituitary adrenal axis suppression and immunosuppression.

The cause of psoriasis is not known, but is believed to involve external or environmental factors that initiate an exaggerated inflammatory response in the skin of genetically predisposed individuals. Following the initial insult an innate immune response is triggered which results in an increase in the production of numerous cytokines. These cytokines promote the accumulation of inflammatory cells in the skin and keratinocyte proliferation (adaptive or acquired immune response). Keratinocytes produce additional inflammatory cytokines, exaggerating the local inflammatory response in the skin of susceptible individuals.

1.2 Brief Discussion of Nonclinical Findings

The systemic toxicity of HBP has been previously addressed by the sponsor in studies to support the approval of Ultravate Cream (NDA 19967, approved 12-27-1990). These studies included 3-month repeat-dose oral toxicity studies in rats and dogs, and studies to address genetic toxicology (Ames, in vitro cytogenetics, in vivo micronucleus, nuclear anomaly, chromosomal aberration, sister chromatid exchange), fertility and early embryonic development in rats and embryofetal development in rats and rabbits. Local toxicity associated with topical use of HBP Lotion (0.05%, 0.1%) was addressed in a 28-day repeat-dose dermal minipig study and with separate studies for acute ocular and dermal irritation. In support of a potential dermal carcinogenicity study, HBP Lotion (0.05%, 0.1%) was applied once daily to rats for 13 weeks (13-2366). Mortality attributed to opportunistic infections resulting from test article-induced immunosuppression occurred at both concentrations. Therefore, the carcinogenicity study was waived since rats would not be able to tolerate long term topical treatment with HBP lotion, 0.05%.

1.3 Recommendations

1.3.1 Approvability

Ultravate Lotion, 0.05% is approvable from a pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. With the exception of titles which are underlined based on the label template, nonclinical recommendations are shown as underlined text. It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the Ultravate Lotion, 0.05% label text. A clean copy of these revised labeling sections is provided in Appendix #1.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

ULTRAVATE Lotion is a corticosteroid indicated for the topical treatment of plaque psoriasis ~~in patients eighteen (18) years of age and older~~.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no (b) (4) data on topical halobetasol propionate use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. (b) (4) Halobetasol propionate administered systemically during organogenesis to rats at 13 and 33 times the human topical dose and to rabbits at 3 times the human topical dose resulted in teratogenic and embryotoxic effects *[see Data]*. The clinical relevance of the animal findings is not clear. (b) (4)

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Halobetasol propionate has been shown to be teratogenic in (b) (4) rats and (b) (4) rabbits when given systemically during (b) (4) organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. These doses are approximately 13, 33, and 3 times, respectively, the human topical dose of halobetasol propionate, 0.05%. Halobetasol propionate was embryotoxic in rabbits but not in rats.

Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats, but not in rabbits.

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action in plaque psoriasis is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

In a 90-day repeat-dose toxicity study in rats, topical administration of halobetasol propionate lotion at dose concentrations from 0.05% to 0.1% or from 0.25 to 0.5 mg/kg/day of halobetasol propionate resulted in a toxicity profile consistent with long-term exposure to corticosteroids including adrenal atrophy, histopathological changes in several organ systems indicative of severe immune suppression, and opportunistic fungal and bacterial infections. A no observable adverse effect level (NOAEL) could not be determined in this study. Although the clinical relevance of the findings in animals to humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis.

Halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the Chinese hamster CHO/HGPRT assay, in the mouse micronucleus test, in the sister chromatid exchange test in somatic cells of the Chinese hamster, or in the chromosome aberration test in somatic cells of Chinese hamsters. Positive mutagenicity effects were observed in two genotoxicity assays: Chinese hamster nuclear anomaly test and mouse lymphoma gene mutation assay in vitro.

Studies in the rat following oral administration at dose levels up to 50 µg/kg/day indicated no impairment of fertility or general reproductive performance.

2 Drug Information

2.1 Drug

CAS Registry Number: 66852-54-8

Generic Name: Halobetasol propionate

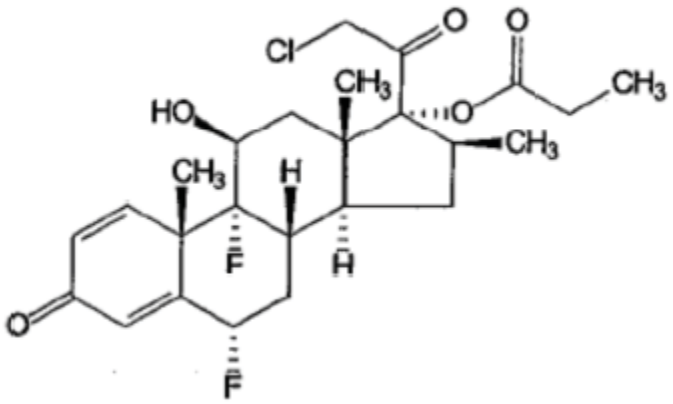
Code Name: ALC 0188

Chemical Name: 21-chloro-6α, 9-difluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate

Molecular Formula/Molecular Weight $C_{25}H_{31}ClF_2O_5$ / 484.96

Structure

3.2.S.1.2 Structure



Pharmacologic Class: Corticosteroid

2.2 Relevant INDs, NDAs, and MFs

IND (b) (4), submitted 11-23-2008

NDA 19967, Ultravate® cream, Ranbaxy Laboratories, Inc., approved 12-27-1990
NDA 19968, Ultravate® ointment, Ranbaxy Laboratories, Inc., approved 12-17-1990

MF (b) (4), halobetasol propionate

2.3 Drug Formulation

The quantitative formulation for Ultravate lotion is provided in the following table.

Ingredient	Purpose	Composition (% w/w)
Halobetasol Propionate USP	API	0.05
Diisopropyl Adipate		(b) (4)
Octyldodecanol, NF		
Ceteth-20		
Poloxamer 407, NF		
Cetyl Alcohol, NF		
Stearyl Alcohol, NF		
Propylparaben, NF		
Butylparaben, NF		
Propylene Glycol, USP		
Glycerin, USP		
Carbomer Homopolymer, NF		
Sodium Hydroxide, NF		(b) (4)
(b) (4) Water, USP		(b) (4)

(b) (4)

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

The sponsor lists three halobetasol propionate degradation products and other impurities, each at a maximum of (b) (4) % (see 3.2.P.5.1 Specifications, taken directly from the submission). The label limits use of the drug product to 50 g/week, or ~ 7g/day. Since the drug product is 0.05% HBP, the amount of drug substance used per day is 3.5 mg (7 g x 0.05%). According to ICH Q3B(R2) if the daily dose of drug substance is <10 mg, the identification threshold is 0.5% or 20 µg TDI, whichever is lower. Thus the impurities are present in the drug product at levels lower than the identification threshold.

3.2.P.5.1Specification(s) Confidential
Halobetasol Propionate (HBP) Lotion 0.05% Page 2 of 2

Test	Method	Bulk	Release	Stability
Impurities and Degradation Products:				
1. (b) (4)				(b) (4)
2.				
3. Any other individual unknown impurities				
4. Total other unknown impurities				
pH				

2.6 Proposed Clinical Population and Dosing Regimen

Ultravate Lotion is indicated for the topical treatment of plaque psoriasis in patients 18 years or older with twice daily dosing for 2 weeks. Treatment beyond two weeks is not recommended and the total dosage should not exceed 50 grams per week.

2.7 Regulatory Background

A pre-IND meeting was not held with the original sponsor, (b) (4) who initially pursued a 505(b)(2) development program with Ultravate® Cream (NDA 19967) or Ultravate® Ointment (NDA 19968) as the listed drug. In 2013, the sponsor obtained a right-of-reference to the original NDA submissions for Ultravate® Cream and Ultravate® Ointment from Ranbaxy Inc., and the development program was transitioned to a 505(b)(1) regulatory pathway.

- July 25, 2012, End-of-Phase 2 meeting
- August 13, 2014, dermal carcinogenicity study waiver granted
- October 27, 2014, pre-NDA meeting

On November 18, 2014 (b) (4) authorized FDA to refer to their Type II DMF # (b) (4) for halobetasol propionate in support of any submission, supplement or amendment filed by Ferndale Laboratories, Inc.

On December 10, 2014, Ranbaxy Inc., provided a letter of authorization to all relevant data in NDA 19967 for Ultravate ® (halobetasol propionate) Cream, 0.05% and in NDA 19968 for Ultravate ® (halobetasol propionate) Ointment, 0.05% to Ferndale Laboratories, Inc.

On December 11, 2014 (b) (4) was transferred from (b) (4) to Ferndale Laboratories, Inc.

3 Studies Submitted

3.1 Studies Reviewed

None

3.2 Studies Not Reviewed

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

Pharmacokinetics

Study under IND (b) (4)

Profiling of metabolites of halobetasol propionate generated by human hepatocytes (MC11M-0013)

Toxicology

Studies under NDA 19967

Three Month Oral Toxicity Study in Beagle Dogs (80-5264)

Three Month Oral Toxicity Study in Rats (80-5225)

Studies under IND (b) (4)

Halobetasol propionate lotion (0.05% and 0.01%): A 13-week dermal toxicity study in rats (13-2366)

Halobetasol propionate lotion: A 4-week dermal toxicity study in Gottingen minipigs (1246-007)

Genetic Toxicity

Studies under NDA 19967

Ames Test for CGP 14458 (32839)

L5178Y/TK$^{+/-}$ Mouse Lymphoma Mutagenicity Test (830399)

CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay (88062)

Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster (830397)

Sister Chromatid Exchange Studies on Somatic Cells of Chinese Hamsters (830398)
Chromosome Studies on Somatic cells of Chinese Hamster (850270)

BMY-30056: Micronucleus Test in Mice (PH 309-BR-001-88)

Reproductive and Developmental Toxicity

Studies under NDA 19967

Reproductive Toxicity Study in Rats (fertility; 830116)

Teratology Study in Rats (FDA Segment II; 840203)

Preliminary Teratology Study in Rabbits (840204)

Special Toxicology Studies

Studies under IND (b) (4)

Primary eye irritation study in rabbits (0421LT28.002)

Primary dermal irritation study in rabbits (0420LT28.010)

3.3 Previous Reviews Referenced

IND (b) (4) Pharmacology/Toxicology reviews

NDA 19967 Pharmacology/Toxicology reviews

4 Pharmacology

4.1 Primary Pharmacology

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.

4.2 Secondary Pharmacology

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

4.3 Safety Pharmacology

No safety pharmacology studies have been conducted with HBP Lotion, 0.05%. However, no adverse effects on the central nervous or respiratory systems were observed in repeat dose toxicity studies performed with rats (13-2366). In the 28-day dermal minipig study (1246-007), no effects on ECG parameters were observed with HBP Lotion, 0.05 and 0.1% when applied twice daily to 10% body surface area.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Halobetasol propionate (1.0, 15.0 µM) was incubated with cryopreserved human hepatocytes and the reaction mixtures were stopped at 0 (pre-incubation), 30, 60, and 120 minutes (MC11M-0013). The samples were analyzed by HPLC. At 1.0 µM, HBP was consumed with a half-life of 33 minutes. Following incubation at 15.0 µM, ten potential metabolites were observed. The most predominant metabolite based on extracted chromatogram peaks was a hydroxylated metabolite. Two other metabolites with notable levels were defluorination metabolites.

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

Dermal toxicity study in minipigs

HBP Lotion (0.05%, 0.1%) was applied twice daily to ~10% total body surface area to Gottingen minipigs (n=4/sex/group) for 28 days (1246-007).

Blood samples (~ 2 mL) were collected from all animals via the anterior vena cava for determination of plasma concentrations predose and ~1, 2, 4, 8, 9, 10, 14, and 24 hours after the first daily dose on Days 1 and 28. Samples were collected in tubes containing K_3EDTA anticoagulant and processed to plasma and shipped on dry ice to (b) (4) , for analysis of plasma concentrations of the test article.

None of the animals in the untreated control group or vehicle control group had any measurable concentrations of HBP. There were no measurable plasma concentrations of HBP on Day 1. On day 28, C_{max}, AUC_{0-24}, AUC_{0-8}, and AUC_{8-24} were higher for males and females receiving 0.1% HBP lotion than for males and females receiving 0.05%

HBP Lotion (see Table 2, Figure 1, taken directly from the study report). There was no evidence of a gender difference.

Table 2. Mean Pharmacokinetic Parameters for Halobetasol Propionate on Day 28

Parameter	Sex	Group	Treatment	Mean ± SD	Median	Range
C_{max} (ng/mL)	M	3	0.05%	0.340 ± 0.405	0.278	0 - 0.804
		4	0.10%	0.815 ± 0.238	0.713	0.663 - 1.17
	F	3	0.05%	0.287 ± 0.333	0.271	0 - 0.607
		4	0.10%	1.01 ± 0.14	1.08	0.803 - 1.09
T_{max} (hr)	M	3	0.05%	9.00 [a]	9.00	9 - 9
		4	0.10%	3.75 ± 5.56	1.50	0 - 12
	F	3	0.05%	6.00 [a]	6.00	2 - 10
		4	0.10%	7.25 ± 4.19	9.00	1 - 10
AUC_{0-24} (ng•hr/mL)	M	3	0.05%	5.45 ± 7.27	3.20	0 - 15.4
		4	0.10%	14.3 ± 2.31	15.0	11.0 - 16.3
	F	3	0.05%	3.66 ± 6.31	0.796	0 - 13.1
		4	0.10%	15.4 ± 7.12	15.5	6.57 - 23.9
AUC_{0-8} (ng•hr/mL)	M	3	0.05%	1.69 ± 2.58	0.660	0 - 5.45
		4	0.10%	5.27 ± 0.76	4.95	4.79 - 6.38
	F	3	0.05%	1.42 ± 2.18	0.536	0 - 4.61
		4	0.10%	5.65 ± 1.89	5.06	4.11 - 8.36
AUC_{8-24} (ng•hr/mL)	M	3	0.05%	3.75 ± 4.76	2.54	0 - 9.92
		4	0.10%	9.05 ± 1.89	9.98	6.21 - 10.0
	F	3	0.05%	2.24 ± 4.15	0.260	0 - 8.45
		4	0.10%	9.70 ± 5.67	10.7	1.94 - 15.5

n = 4, except as noted. Standard deviation values were not calculated when n < 3.

[a] n = 2

The clinical observations and toxicities noted in this study were consistent with the known effects of corticosteroids and included adrenal atrophy, bone marrow hypocellularity and minimal to severe generalized lymphoid depletion in lymph nodes, GALT, spleen, thymus gland. Based on these data, HBP lotion at concentrations of 0.05% (the clinical concentration) and 0.10% did not produce any new or unique toxicity that has not been previously observed with corticosteroid drugs.

<u>13-week dermal dose range-finding study in rats</u>

HBP Lotion (0.05%, 0.1%) was applied once daily to ~10% total body surface area to Sprague-Dawley rats (n = 15/sex/group) for 13 weeks (13-2366) in a dose range-finding study for an eventual 2-year dermal carcinogenicity study. Dermal administration resulted in expected pharmacologic effects that were generally exaggerated and adverse. Mortality attributed to opportunistic infections resulting from test article-

induced immunosuppression, occurred at both concentrations. Animals at both concentrations failed to gain weight and consumed less feed compared to controls. A NOAEL could not be determined.

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

Oral toxicity study in rats

Organ weight changes included dose-related decreases in liver, adrenal, spleen, and thymus weights in all oral HBP rat groups treated daily for 3 months. These decreases were statistically significant at 0.1 and 1 mg/kg/day and often at 0.01 mg/kg/day. No marked resolution in organ weights was noted following the 1-month recovery period. A dose-related increase in the severity of microscopic changes was noted. At 0.01 mg/kg/day, minimal atrophy of the adrenal gland and minimal reduction of lymphatic elements in the thymus, spleen, and lymph nodes were noted. At 0.1 and 1 mg/kg/day, these changes progressed to marked atrophy in the adrenal gland and thymus, ballooned hepatocytes with fatty degeneration in the liver, marked reduction in lymphatic parenchyma in the spleen and lymph nodes, and an increased incidence of respiratory infections. After recovery, the effects either improved (high-dose group) or recovered (mid-dose group). The effects observed are considered to be typical of corticosteroids. The NOAEL was 0.01 mg/kg/day.

Oral toxicity study in dogs

Beagle dogs (n=3/sex/group) were administered HBP orally via capsules at doses of 0, 0.01, 0.03, and 0.1 mg/kg/day for 3 months (805264). An additional 3 males and 3 females were included in the high-dose group and maintained for a 1-month recovery period. Parameters evaluated included clinical signs, body weight, feed consumption, clinical pathology ophthalmoscopy, electrocardiography, neurological assessments, hearing, gross pathology, organ weights and histopathology (all animals in all groups). There were no test article-related mortalities. Body weight was decreased at 0.1 mg/kg/day with weight loss occurring in 8 out of 12 high-dose animals. Recovery was noted during the follow-up recovery period. Feed consumption was unaffected.

Adrenal weight was reduced (all doses), and liver (all doses) and spleen (high dose) weights were increased. Other organ weight changes did not have a microscopic correlate. Histopathological evaluation revealed a dose-related increase in the severity of changes. At 0.01 mg/kg/day, a few scattered hepatocytes with ballooning/vacuolization were noted with marked adrenal atrophy (females) and thymic atrophy, and minimal urogenital tract inflammation. At 0.03 and 0.1 mg/kg/day, more numerous ballooned and vacuolated hepatocytes were observed with marked atrophy of the adrenals and thymus, reduced lymphatic elements in the spleen and lymph nodes, and an increased inflammatory reaction in the urogenital tract. In the high-dose

dogs, the microscopic changes either resolved or improved during the recovery period, except for the adrenal gland. A NOAEL was not identified in this study.

7 Genetic Toxicology

The sponsor has obtained the right of reference to the genetic toxicology studies conducted to support Ultravate® Cream, 0.05% (NDA 19967). The following information appears in the Mutagenesis section of the label for Ultravate® Cream, 0.05% (NDA 19967).

Positive mutagenicity effects were observed in two genotoxicity assays. Halobetasol propionate was positive in a Chinese hamster micronucleus test, and in a mouse lymphoma gene mutation assay in vitro. In other genotoxicity testing, halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the sister chromatid exchange test in somatic cells of the Chinese hamster, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test to determine point mutations.

8 Carcinogenicity

Data from a 13-week rat dermal study (13-2366) showed that HBP Lotion 0.05% and 0.1% caused marked immunosuppression in animals resulting in the development of opportunistic infections as well as significant toxicity in multiple organ systems after receiving only 13 weeks of daily dermal dosing. The anticipated survivability and general health concerns preclude conduct of a 2-year dermal carcinogenicity study on 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 should be incorporated into Section 13.1 of the Ultravate lotion label.

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

9 Reproductive and Developmental Toxicology

The sponsor has obtained the right of reference to the fertility and embryofetal development studies conducted to support Ultravate® Cream, 0.05% (NDA 19967). The following information appears in the corresponding sections of the label for Ultravate® Cream, 0.05% (NDA 19967).

9.1 Fertility and Early Embryonic Development

Studies in the rat following oral administration at dose levels up to 50 µg/kg/day indicated no impairment of fertility or general reproductive performance.

9.2 Embryonic Fetal Development

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. Halobetasol propionate has been shown to be teratogenic in SPF rats and chinchilla-type rabbits when given systemically during gestation at doses of 0.04 to 0.1 mg/kg in rats and 0.01 mg/kg in rabbits. These doses are approximately 13, 33, and 3 times, respectively, the human topical dose of halobetasol propionate, 0.05%. Halobetasol propionate was embryotoxic in rabbits, but not rats.

Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats, but not in rabbits.

10 Special Toxicology Studies

HBP Lotion, 0.05% was not a dermal irritant in rabbits after a 4-hour application (0420LT28.010). HBP Lotion, 0.05% was slightly irritating to the rabbit eye (0421LT28.002).

11 Integrated Summary and Safety Evaluation

Topical repeat-dose toxicity studies conducted using the clinical HBP formulation (0.05%) and an enhanced formulation (0.1%) 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 in rats and dogs, 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.

Ultravate Lotion, 0.05% 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

ULTRAVATE Lotion is a corticosteroid indicated for the topical treatment of plaque psoriasis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on topical halobetasol propionate use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. Halobetasol propionate administered systemically during organogenesis to rats at 13 and 33 times the human

topical dose and to rabbits at 3 times the human topical dose resulted in teratogenic and embryotoxic effects *[see Data]*. The clinical relevance of the animal findings is not clear.

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Halobetasol propionate has been shown to be teratogenic in rats and rabbits when given systemically during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. These doses are approximately 13, 33, and 3 times, respectively, the human topical dose of halobetasol propionate, 0.05%. Halobetasol propionate was embryotoxic in rabbits but not in rats.

Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats, but not in rabbits.

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 plaque psoriasis is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

In a 90-day repeat-dose toxicity study in rats, topical administration of halobetasol propionate lotion at dose concentrations from 0.05% to 0.1% or from 0.25 to 0.5 mg/kg/day of halobetasol propionate resulted in a toxicity profile consistent with long-term exposure to corticosteroids including adrenal atrophy, histopathological changes in several organ systems indicative of severe immune suppression, and opportunistic fungal and bacterial infections. A no observable adverse effect level (NOAEL) could not be determined in this study. Although the clinical relevance of the findings in animals to humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis.

Halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the Chinese hamster CHO/HGPRT assay, in the mouse micronucleus test, in the sister chromatid exchange test in somatic cells of the Chinese hamster, or in the chromosome aberration test in somatic cells of Chinese hamsters. Positive mutagenicity effects were observed in two genotoxicity assays: Chinese hamster nuclear anomaly test and mouse lymphoma gene mutation assay in vitro.

Studies in the rat following oral administration at dose levels up to 50 µg/kg/day indicated no impairment of fertility or general reproductive performance.

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/s/

JILL C MERRILL
08/19/2015

BARBARA A HILL
08/19/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 208183 **Applicant:** Ferndale Laboratories, Inc. **Stamp Date:** 01/08/2015

Drug Name: halobetasol propionate lotion, 0.05% **NDA Type:** 505(b)(1)

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	Y		Formatted to allow substantive review.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	Y		Indexed and paginated to allow substantive review.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	Y		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	Y		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	Y		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	Y		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	Y		Under Section 2.4.1 the sponsor states: All studies conducted by the sponsor were compliant with Good Laboratory Practices (GLPs)….With respect to the toxicology studies conducted on HBP alone, all were GLP-compliant except the Ames assay and the embryofetal development study in rabbits, both of which were pilot studies. These studies also followed generally

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
				accepted study designs, particularly at the time they were performed. Any missing data (e.g. toxicokinetics) did not affect the ability to draw safety conclusions about the drug.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Y		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	Y		Section 8 is written using the old format. The sponsor will be asked to revise Section 8 of the label to be consistent with the new PLLR format.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	Y		
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 60-day letter.

None.

It is recommended that the following comment be relayed to the sponsor in the 74-day letter.

We recommend that your proposed prescribing information conform to the FDA published *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule (PLLR or final rule).

Jill Merrill 02-12-2015
Reviewing Pharmacologist Date

Barbara Hill see sign-off date
Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

JILL C MERRILL
02/23/2015

BARBARA A HILL
02/23/2015

Memorandum

To: IND (b) (4)
From: Jill C Merrill
Re:
SDN: 57, 58
Date: July 9, 2014; July 15, 2014

Type: nonclinical information
Drug: Halobetasol Propionate Lotion, 0.05%
Sponsor: (b) (4)
Indication: moderate to severe plaque psoriasis

Information to sponsor: yes

Review date: 8-7-2014

Background:

The sponsor submitted an IND for a potential 505(b)(2) approval of a novel formulation containing 0.05% halobetasol propionate (HBP) for the topical treatment of moderate to severe plaque psoriasis (11-23-2008). The active ingredient is well characterized and the concentration is known to be safe and effective as a topical anti-inflammatory and antipruritic agent in different formulations approved by the FDA. The sponsor was informed (12-19-2008) that given the long history of safe use of multiple HBP formulations and assuming an adequate clinical bridge could be established to a previously approved HBP formulation (*i.e.*, Ultravate® Cream, NDA 19967) it was acceptable to use the Agency's findings of safety to support the systemic safety of their topical formulation and use the 505(b)(2) regulatory approval pathway. However, a dermal carcinogenicity study would be needed to support an NDA submission of the drug product.

During the end-of-phase 2 (EoP2) meeting (July 25, 2012) the protocol for the 13-week dermal range finding study to support an eventual 2-year dermal carcinogenicity study was discussed. The Agency agreed that it was acceptable to use two concentrations of the active in the to-be-marketed formulation with daily treatment to 10% of the body surface area (BSA). If results from an appropriately conducted dermal range finding study suggested that the 2-year study would not be feasible, the sponsor was advised to submit a waiver request.

Information contained in SDN57 and SDN58:

In SDN57 (July 9, 2014), the sponsor submitted the final study report entitled "Halobetasol Propionate Lotion (0.05% and 0.1%): A 13-week dermal toxicity study in rats". This study is reviewed below. In SDN58 (July 15, 2014), the

sponsor submitted a waiver request for conduct of the 2-year dermal carcinogenicity study, based on results obtained during the 13-week study.

Study title: Halobetasol Propionate Lotion (0.05% and 0.1%): A 13-week dermal toxicity study in rats

Study no.:	13-2366
Study report location:	IND (b) (4), SDN57
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 9, 2013
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	HBP Lotion 0.05%, 13082A, as per CoA meets specifications HBP Lotion 0.1%, PC13009, as per CoA meets specifications HBP Vehicle Lotion, 13081A, as per CoA meets specifications

Key Study Findings

Dermal administration of HBP lotion to rats at concentrations of 0.05% and 0.1% for 13 weeks resulted in expected pharmacologic effects that were generally exaggerated and adverse. Mortality, attributed to opportunistic infections resulting from test article-induced immunosuppression, occurred at both concentrations and animals at both concentrations failed to gain weight and consumed less feed compared to controls. A NOAEL could not be determined.

Methods

Doses:	[redacted] (b) (4), vehicle control, 0.05%, 0.1% HBP Lotion)
Frequency of dosing:	[redacted] (b) (4)
Route of administration:	Topical to clipped dorsal area (~10% BSA)
Dose volume:	0.5 mL/kg
Formulation:	Clinical formulation
Species/Strain:	Rat / Sprague-Dawley
Number/Sex/Group:	15
Age:	~ 8 weeks
Weight:	Males: 228 – 292 g; females: 176 – 233 g
Satellite groups:	Toxicokinetics
Unique study design:	Restricting the study to two test concentrations (clinical and maximum feasible) was discussed and approved by the Agency during the EoP2 meeting (July 25, 2012).
Deviation from study protocol:	None critical to validity and integrity of study results

	Daily Dose Application Information [a]			Number of Animals							
				Total on Study		Toxicity Study				TK Study[b]	
						Total		Terminal Necropsy		Days 1 and 90	
Group	Body surface area	Dose Volume (mL/kg)	Concentration (%)	M	F	M	F	M	F	M	F
1 (untreated control)	-	-	-	15	15	15	15	15	15	0	0
2 (vehicle control)	10%	0.50	0	18	18	15	15	15	15	3	3
3	10%	0.50	0.05	24	24	15	15	15	15	9	9
4	10%	0.50	0.1	24	24	15	15	15	15	9	9

[a]Specific gravity of the vehicle lotion =0.98 g/mL.

[b]Toxicokinetic samples will be collected on Days 1 and 90. Refer to Section 10.7 for more detailed information regarding sample collection times and procedures.

0.1%: 0.5mL/kg x 0.98 g/mL x 0.1% = 0.49 mg/kg
0.05%: 0.5 mL/kg x 0.98 g/mL x 0.05%= 0.245 mg/kg

Observations and Results

Mortality

Animals were observed twice daily for mortality and general condition. Test article-related unscheduled deaths occurred in both sexes at both HBP concentrations (Text Table 3.2-1, taken directly from the study report). In the

0.05% HBP animals (Group 3), 2 toxicity animals (1 male and 1 female) and a toxicokinetic (TK) male were found dead and 1 male and 1 female in the TK phase were euthanized moribund. In the 0.1% HBP animals (Group 4), 5 males and 2 females in the toxicity group were euthanized moribund and 2 toxicity males were found dead, 3 males and 1 female in the TK were euthanized moribund, 1 TK male was found dead and 1 was euthanized moribund. All early mortalities in the high-dose females (Group 4) were due to moribund termination. One vehicle control male was observed with splayed hind limbs, abnormal gait and chromodacryorrhea and euthanized moribund on Day 55. A cause of death could not be established.

Text Table 3.2-1: Unscheduled death

Formulation Concentration	**0.05%**		**0.1%**	
Gender	**M**	**F**	**M**	**F**
Toxicity Study	1	1	7	2
Animal Numbers	3074	3613	4082, 4083, 4086, 4089,4091, 4092, 4094	4568, 4569
Toxicokinetic	2	1	5	1
Animal Numbers	3084, 3087	3611	4096, 4097,4099, 4100, 4101	4576

All unscheduled deaths were attributable to one or more opportunistic bacterial and/or fungal infections facilitated by the immunosuppressive effects of HBP. Pronounced lymphoid depletion in the thymus and secondary lymphoid tissues (spleen, lymph nodes, and gut-associated lymphoid tissue (GALT) was observed in most unscheduled decedents indicating test article-associated profound immunosuppressive effects. Salient necropsy and histopathology findings from the unscheduled decedents are summarized in the Text Table 3.9-1, taken directly from the study report.

Text Table 3.9-1: Test article-related Unscheduled Mortality - Summary of Salient Findings

Animal No./Gender/Test Article Concentration (%) Nature of Death/Day of Death	Select Necropsy Findings	Histopathology Findings	Cause of Unscheduled Mortality
4092/Male/0.1 Welfare Euthanasia /Day 42	Kidneys: Mass, bilateral Liver: Mass, right anterior & median lobes	Kidney: Acute Inflammation Liver: Inflammation, necrotizing Brain: Acute Inflammation All lesions associated with numerous bacterial colonies	Septicemia (Opportunistic)
4082/Male/0.1/ Welfare Euthanasia/Day 62	Kidney: Discoloration, tan, left	Kidney: Pyelonephritis	Pyelonephritis (Opportunistic)
4083 /Male/0.1 Welfare Euthanasia/Day 84	Raised areas, lungs, liver	Lungs: pyogranulomatous inflammation associated with fungal hyphae Brain: Meningoencephalitis	Opportunistic infections
4086 /Male/0.1 Welfare Euthanasia/Day 57	Kidney: Pale areas, left	Kidney: Pyelonephritis Brain: Meningoencephalitis, Necrotizing associated with fungal hyphae	Opportunistic infections
4089/Male/0.1 Found Dead/Day 26	Kidney: Discoloration, red, medulla, dilated pelvis Lung: tan area R middle lobe	Kidney: Pyelonephritis Lungs: pyogranulomatous inflammation associated with fungal hyphae	Opportunistic infections

Animal No./Gender/Test Article Concentration (%) Nature of Death/Day of Death	Select Necropsy Findings	Histopathology Findings	Cause of Unscheduled Mortality
4091/Male/0.1 Found Dead/Day 73	Kidney: Pale raised areas Liver: Mass, left lobe	Kidney: Acute inflammation Liver: Inflammation, necrotizing, Brain: Acute inflammation All lesions associated with bacterial colonies	Septicemia (Opportunistic)
4094 /Male/0.1 Welfare Euthanasia/Day 63	Kidney: Dark red areas	Kidney: Pyelonephritis	Pyelonephritis (Opportunistic)
4568 /Female/0.1 Welfare Euthanasia /Day 82	Lung: Mass	Lungs: Inflammation, Necrotizing associated with fungal hyphae	Opportunistic infection
4569 /Female/0.1 Welfare Euthanasia /Day 89	Trachea: Mass	Trachea: Inflammation, Necrotizing associated with fungal hyphae	Opportunistic infection
3613/Female/0.05 Found Dead/Day 45	Kidney: White areas, bilateral	Kidney: Acute inflammation associated with bacterial colonies	Septicemia (Opportunistic)
3074/Male/0.05/ Found Dead/Day 89	Lung: Mass, Right caudal lobe Trachea: Mass	Lungs: Inflammation, Necrotizing associated with fungal hyphae Trachea: Inflammation, Necrotizing; associated with fungal hyphae Kidney: Pyelonephritis	Opportunistic infections

Animal No.2032, a vehicle control male was humanely euthanized on Day 55. Necropsy findings in this unscheduled decedent was limited to red discoloration of multiple lymph nodes that correlated microscopically with sinus erythrocytosis/erythrophagocytosis. A cause of mortality was not established based on necropsy and histopathology observations.

Clinical Signs

Toxicity animals were observed once weekly for general condition and external evaluation of eyes, nose, skin, fur, oral cavity, abdomen, and external genitalia. The most-consistent test article-related clinical observations noted were red discoloration in the urine and thin appearance in both sexes at ≥0.05% HBP concentrations. Less frequently, impaired locomotion and hunched posture were also observed in treated animals. Test article-related dose site dermal observations included erythema, atonia (decrease in elasticity), desquamation (scaling and flaking of the skin) and/or eschar (scab formation) at ≥0.05% HBP concentrations.

Body Weights

Animals were weighed weekly. A statistically significant suppression of body weight gain was reported at ≥ 0.05% concentrations with males and females in Groups 3 and 4 gaining minimal to no weight over the course of the study (Figure 1 and 2; taken directly from the study report). Differences in terminal body weights were similar at both concentrations and did not follow a dose trend.

Mean body weight and body weight gains were lower for the vehicle treated males beginning Week 7 until study termination. Mean body weights at study termination were as much as 59% (males) and 35% (females) lower than mean body weights in the control animals.

FIGURE 1 Body weight - males

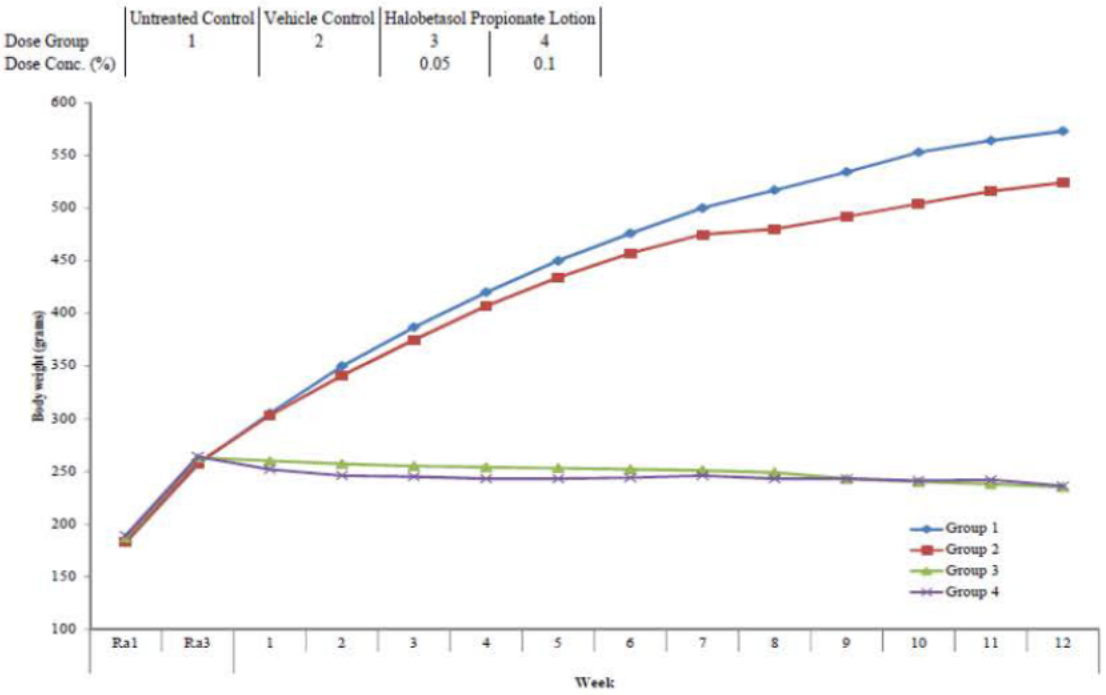
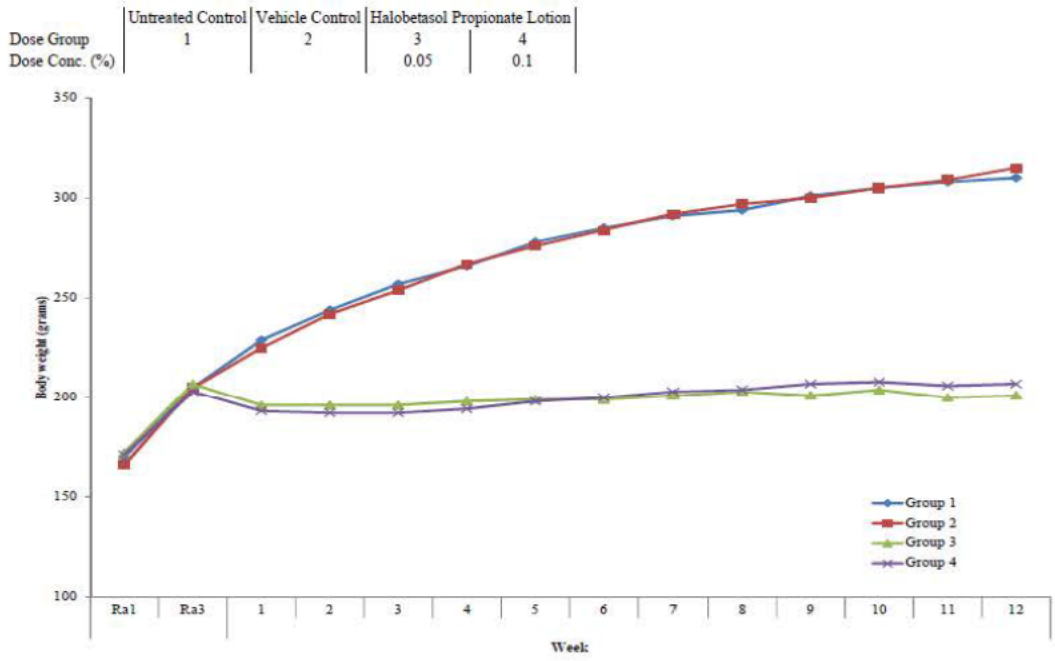


FIGURE 2 Body weight - females



Feed Consumption

Feed consumption was measured weekly. Feed consumption was significantly reduced in both sexes at ≥0.05% HBP concentrations (males: up to -46% and females: up to -21% versus untreated and vehicle control groups) throughout the study.

Ophthalmoscopy

All animals were examined pretest and at study termination. Lids, lacrimal apparatus and conjunctiva were examined visually. The cornea, anterior chamber, lens, iris, vitreous humor, retina and optic disc were examined by indirect ophthalmoscopy. The pupils of each eye were dilated prior to examination using tropicamide ophthalmic solution. Based on the pretest ocular examination of 170 rats, 2 males and 2 females were excluded from the study. At study termination (110 rats), there were no test article-related ocular abnormalities.

ECG

Not performed.

Hematology

Blood samples were collected into tubes containing K_3EDTA anticoagulant and analyzed for the following parameters: hemoglobin concentration, hematocrit, erythrocyte count, platelet count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, total leukocyte count, reticulocyte count, differential leukocyte count (neutrophils, lymphocytes, eosinophils, basophils, monocytes, large unstained cells). Blood samples were collected into tubes containing sodium citrate anticoagulant and analyzed for prothrombin time, and activated partial thromboplastin time.

The main test article-related hematologic findings were moderate to marked decreases in total white blood cells (due to decreased lymphocytes, eosinophils and basophils), minimal decreases in platelets and red blood cell count, and slight increases in mean cell volume (MCV) and neutrophils in both sexes at ≥0.05% HBP. Decreases in lymphocyte counts were considered to be expected/exaggerated pharmacologic effects of the test article, a synthetic glucocorticoid, and were considered to be adverse based on resulting immunosuppression and infections leading to mortality. Lymphocyte decreases correlated with decreased serum globulins, decreased lymphoid organ weights and size (spleen and thymus) and with cellular depletion of all lymphoid organs, and with secondary opportunistic infections. Red blood cell, platelet, eosinophil and basophil decrease correlated with decreased bone marrow cellularity (slight to severe).

In females, statistically significant decreases in mean hemoglobin and hematocrit were primarily due to moderate decreases in Animal # 3589, 4563 and 4573 (hematocrit = 26.7%, 23.1%, 29.2%, respectively). Animal # 4563 and 4573 also had increased reticulocytes, mean cell volume (MCV) and red cell distribution width (RDW), and decreased mean cell hemoglobin concentration (MCHC) consistent with regenerative response and correlating with moderately increased splenic extramedullary hematopoiesis. Animal # 4563 had a moderate increase in total white blood cells (including neutrophils, lymphocytes, and monocytes) which correlated with ulceration, abscess formation and inflammation of the extremities and inflammation in the lungs and bronchi.

Text Table 3.7.2-1: Halobetasol Propionate-related hematology changes in rats dosed for 13 weeks[a]

Sex	Males		Females	
Dose (%)	0.05	0.1	0.05	0.1
RBC	-11%	-11%	-14%	-21%
Platelets	-22%	-27%	-25%	-22%
MCV	+9.2%	+9.5%	+9.3%	+12%
WBC	-42%	-39%	-50%	-18%
Neutrophils	2.2X	2.5X	2.2X	4.0X
Lymphocytes	-87%	-92%	-86%	-83%
Eosinophils	-82%	-59%	-91%	-73%
Basophils	-75%	-100%	-100%	-67%

RBC: red blood cells; MCV: mean corpuscular volume; WBC: total white blood cells.
[a]: Decreases and increases <2X expressed as percent change versus concurrent control. Increases ≥2X expressed as fold change versus control. Means were statistically significant when compared to untreated controls.

Shortened mean prothrombin and prolonged mean activated partial thromboplastin times were observed in males at ≥0.05% topically applied HBP. These changes were statistically significant and dose-related, but minimal in severity.

Clinical Chemistry

Blood samples were collected into tubes containing no anticoagulant, allowed to clot, centrifuged to obtain serum and analyzed for the following parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, blood urea nitrogen, creatinine, glucose, cholesterol, triglycerides, total protein, albumin, total bilirubin, sodium, potassium, chloride, calcium, inorganic phosphorus.

Test article-related changes included minimal to moderate increases in AST, ALT, cholesterol, and triglycerides and minimal decreases in creatinine and globulins (sometimes affecting total proteins and albumin to globulin ratio) in both sexes at ≥0.05% HBP (Table 3.7.4-1, taken directly from the study report). These changes were considered to reflect expected/exaggerated pharmacologic effects of the test article. Metabolic effects included increases in AST, ALT,

cholesterol, and triglycerides and minimal decreases in creatinine. Immunosuppresssive effects were limited to decreases in globulins.

Text Table 3.7.4-1: Halobetasol Propionate-related clinical chemistry changes in rats dosed for 13 weeks[a]

Sex	Males		Females	
Dose (%)	0.05	0.1	0.05	0.1
AST	73%	63%	2.3X	2.4X
ALT	3.8X	4.2X	6.5X	7.3X
Creatinine	-33%	-33%	-33%	↑↓ (0%)
Cholesterol	2.4X	2.9X	98%	94%
Triglycerides	2.4X	4.3X	2.0X	2.7X
TP	-7.0%	-7.0%	-5.6%[ns]	-8.3%
Globulin	-20%	-20%	-13%	-13%
A/G	21%	21%	14%	14%

AST: aspartate aminotransferase; ALT: alanine aminotransferase; TP: total protein; A/G: albumin:globulin ratio.
[a] : Decreases and increases <2X expressed as percent change versus concurrent control. Increases ≥2X expressed as fold change versus control. Means were statistically significant when compared to controls, unless otherwise indicated.
[ns]: not statistically significant

Urinalysis

Urine was collected into ice-chilled containers overnight (~16 hours) from animals housed in metabolism cages and analyzed for the following parameters: pH, protein, glucose, ketones, bilirubin, urobilinogen, occult blood appearance, specific gravity, volume. When the protein result was ≥100 mg/dL microscopic examination of the urine sediment was performed on centrifuged urine samples and the following cellular elements were identified: blood, sperm, erythrocytes, leukocytes, epithelial cells, casts, amorphous matter, and crystals.

The most notable finding was the presence of decreased clarity and or red urine with increased protein, ketones, bilirubin, and/or occult blood in both sexes at ≥0.05% topically applied HBP. Microscopic examination indicated that there was an active sediment which contained white blood cells and red blood cells. Findings correlated with increased incidence and severity of hyaline casts and the presence of marked acute inflammation and slight to severe pyelonephritis in the kidneys. These changes were considered to be secondary to test article-related immunosuppression and infection.

Gross Pathology

Animals were terminated by exsanguination following isoflurane inhalation. Scheduled necropsy was performed on overnight fasted animals and included examination of the external surface and all orifices, the external surfaces of the brain and spinal cord, the organs and tissues of the cranial, thoracic, abdominal and pelvic cavities and neck and the remainder of the carcass for the presence of macroscopic morphologic abnormalities.

The most consistent findings at necropsy in animals treated with ≥ 0.05% HBP were small adrenal glands, thymus and spleen (Table 3.9.1-1, taken directly from

the study report). These macroscopic findings correlated with the microscopic findings described below.

Text Table 3.9.1-1: Test Article-Related Selected Macroscopic Observations

Group/sex	*1M*	*2M*	*3M*	*4M*	*1F*	*2F*	*3F*	*4F*
Halobetasol Propionate Conc. (%)	**0**	**0**	**0.05**	**0.1**	**0**	**0**	**0.05**	**0.1**
Topical Application Site [a]	**15**	**14**	**14**	**8**	**15**	**15**	**14**	**13**
Thin	0	0	6	5	0	0	11	12
Adrenal Gland [a]	**15**	**14**	**14**	**8**	**15**	**15**	**14**	**13**
Small	0	1	13	8	0	0	10	10
Thymus [a]	**15**	**14**	**14**	**8**	**15**	**15**	**14**	**13**
Small	0	0	13	5	0	0	8	10
Spleen [a]	**15**	**14**	**14**	**8**	**15**	**15**	**14**	**13**
Small	0	0	14	8	0	0	12	10
Lungs & Bronchi [a]	**15**	**14**	**14**	**8**	**15**	**15**	**14**	**13**
Pale areas	0	0	10	7	0	0	8	12
Adipose Tissue [a]	**0**	**1**	**6**	**5**	**0**	**0**	**9**	**9**
Thickened	0	0	6	5	0	0	9	9

[a] = Number of tissues examined from each group

Organ Weights

Adrenal glands, brain (medulla, pons, cerebrum, cerebellum), epididymides, heart, kidneys, liver, ovaries (with oviducts), pancreas, pituitary gland, prostate gland, seminal vesicles, spleen, testes, thymus, thyroid/parathyroid glands, uterus (body/horns) with cervix.

Test article-related, statistically significantly lower mean absolute and relative (to brain and body weight) spleen, adrenal and uterus/cervix weights, relative to control values, were observed at HBP concentrations ≥0.05%. Statistically significant, lower mean thymus and ovaries/oviducts weights (absolute and relative to brain weight), compared to control values observed at ≥0.05% were also attributed to the test article. These organ weight differences were considered to be the result of exaggerated pharmacologic effects of HBP. Test article-related organ weight differences are summarized in Text Table 3.8-1, taken directly from the study report.

Text-Table 3.8-1: Test article-related organ weight differences (approximate % difference in mean values relative to controls) at terminal sacrifice

	Males		Females	
Halobetasol Propionate Concentration (%)	**0.05**	**0.1**	**0.05**	**0.1**
No. Examined	**14**	**8**	**14**	**13**
Adrenal Gland				
absolute	-67%[a]	-70%[a]	-72%[a]	-73%[a]
vs body weight	-14%	-25%[a]	-54%[a]	-57%[a]
vs brain weight	-63%[a]	-65%[a]	-69%[a]	-70%[a]
Spleen				
absolute	-78%[a]	-80%[a]	-63%[a]	-55%[a]
vs body weight	-43%[a]	-50%[a]	-39%[a]	-26%[a]
vs brain weight	-75%[a]	-77%[a]	-59%[a]	-49%[a]
Thymus				
absolute	-62%[a]	-51%[a]	-44%[a]	-39%[a]
vs body weight	-	-	-9.0%	-
vs brain weight	-57%[a]	-43%[a]	-38%[a]	-31%[a]
Ovaries/Oviducts				
absolute	N/A	N/A	-36%[a]	-33%[a]
vs body weight			-	-
vs brain weight			-29%[a]	-24%[a]
Uterus/Cervix				
absolute	N/A	N/A	-62%[a]	-58%[a]
vs body weight			-38%[a]	-32%[a]
vs brain weight			-58%[a]	-52%[a]

[a]Statistically significant difference between mean values for test article-treated and control groups
Dash '-'= no test article-related effect.
vs = versus
N/A = Not Applicable

Weight differences in the following organs were statistically significant when compared to the control group, but were considered to reflect test article-related differences in terminal body weights (lower than control weights): brain, heart, kidneys, liver, pancreas, pituitary, epididymides, testes, prostate, seminal vesicles, thyroid and parathyroid.

Histopathology

The following tissues were retained and preserved from all toxicity animals, but only examined microscopically in all animals from Groups 1, 2, and 4: adrenal glands, aorta, bone (sternum, femur including joint), bone marrow smear (femur), brain (medulla, pons, cerebrum and cerebellum),dose site and untreated site (cervical dorsal unclipped area), epididymides, esophagus, eyes, Harderian gland, heart, kidneys, lacrimal glands, large intestine (cecum, colon, rectum), liver, lungs (with mainstem bronchi), lymph nodes (mesenteric, axillary), mammary gland (inguinal), nerve (sciatic), ovaries (with oviducts), pancreas, pituitary gland, prostate gland, salivary glands (mandibular), skeletal muscle (*rectus femoris*), seminal vesicles, skin (dorsal- base of tail), small intestine (duodenum, ileum, jejunum, and Peyer's patches/GALT), spinal cord (cervical,

thoracic, lumbar), spleen, stomach, testes, thymus, thyroid/parathyroid glands, trachea, urinary bladder, uterus (body/horns) with cervix, vagina, tissues with macroscopic findings including tissue masses.

Adequate Battery- yes

Histological Findings
Microscopic findings associated with topical administration of HBP included cellular depletion in all lymphohematopoietic organs with secondary opportunistic infections at ≥0.05% and atrophy of the adrenal gland, skin, and female reproductive organs at 0.1%. Test article-related findings were also observed in the liver, lungs, mammary gland, femur, adipose tissue and pancreas. The wide array of HBP-related microscopic findings were largely the result of corticosteroid-associated anti-proliferative, immunosuppressive and androgenic/anti-estrogenic effects.

Lymphohematopoietic tissues: Pronounced lymphoid depletion was observed in the thymus, spleen, lymph nodes and GALT at ≥0.05% HBP in both genders (Table 3.9.2-1, taken directly from the study report). A marked to severe decrease in the density of lymphocyte populations was observed in both the cortex and medulla of the thymus. Similarly, there was moderate to marked atrophy of the white pulp of spleen and general decrease in cellularity (slight to marked) of the cortex, paracortex and follicles of the mesenteric and axillary lymph nodes. Microscopic findings in the thymus and spleen correlated with lower organ weights and necropsy observations of diminished organ size. Lymphoid depletion was an anticipated effect of the systemic absorption of HBP. Decreased cellularity characterized by a general decrease in myeloid, erythroid and megakaryocytic lineage cells was observed in the marrow of the sternum and femur in both genders at 0.1% HBP (bone marrow from the 0.05% groups was not evaluated microscopically). Hematopoietic precursor cell populations were moderately to markedly decreased in the majority of females at 0.1% HBP, while males were generally less severely affected.

Text Table 3.9.2-1: Incidence and Severity of Selected Test Article-Related Histopathologic Findings in the Lymphohematopoietic Tissues -Terminal Sacrifice

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Halobetasol Propionate Conc. (%)	**0**	**0**	**0.05**	**0.1**	**0**	**0**	**0.05**	**0.1**
Spleen [a]	15	14	14	8	15	15	13	13
Atrophy, White Pulp								
Moderate	0	0	1	0	0	0	2	1
Marked	0	0	10	6	0	0	11	11
Severe	0	0	3	2	0	0	0	1
Thymus [a]	15	14	12	4	15	15	12	13
Decreased, Generalized Cellularity								
Marked	0	0	6	0	0	0	11	5
Severe	0	0	6	4	0	0	1	8
Lymph Node, Axillary [a]	14	13	11	3	15	15	11	13
Decreased, Generalized Cellularity								
Minimal	0	0	1	0	0	0	0	0
Slight	0	0	1	0	0	0	5	3
Moderate	0	0	7	0	0	0	3	6
Marked	0	0	2	3	0	0	0	4
Lymph Node, Mesenteric [a]	15	14	12	8	15	15	13	13
Decreased, Generalized Cellularity								
Slight	0	0	3	0	0	0	4	7
Moderate	0	0	9	4	0	0	7	6
Marked	0	0	0	3	0	0	1	0
Peyer's Patches/GALT [a]	15	14	7	8	15	15	2	11
Cellularity, Decreased								
Slight	0	0	0	0	0	0	0	1
Moderate	0	0	5	4	0	0	1	8
Marked	0	0	2	1	0	0	1	2
Bone Marrow, Femoral [a]	15	14	0	7	15	15	0	13
Cellularity, Decreased								
Slight	0	0	0	5	0	0	0	0
Moderate	0	0	0	0	0	0	0	6
Marked	0	0	0	0	0	0	0	5

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Halobetasol Propionate Conc. (%)	**0**	**0**	**0.05**	**0.1**	**0**	**0**	**0.05**	**0.1**
Bone Marrow, Sternum [a]	15	14	0	8	15	15	0	13
Cellularity, Decreased								
Slight	0	0	0	1	0	0	0	1
Moderate	0	0	0	5	0	0	0	1
Marked	0	0	0	2	0	0	0	8
Severe	0	0	0	0	0	0	0	2

[a] = Number of tissues examined from each group

Adrenal cortex: HBP-related atrophy of the adrenal cortex was observed at ≥0.05% HBP in both genders (Table 3.9.2-2, taken directly from the study report). The adrenal cortex was characterized by a pronounced decrease in thickness of the zona fasciculata. Cells of the zona fasciculata were generally diminished in size and had decreased cytoplasmic vacuolation compared to control animals. A relative increase in the prominence of intervening sinusoids was also observed. Atrophy of the adrenal cortex correlated with lower adrenal weights and with the macroscopic observation of small adrenal glands.

Text Table 3.9.2-2: Incidence and Severity of Selected Test Article-Related Histopathologic Findings in the Adrenal-Terminal Sacrifice

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Halobetasol Propionate Conc. (%)	0	0	0.05	0.1	0	0	0.05	0.1
Adrenals [a]	15	14	14	8	15	15	13	13
Atrophy, Cortical								
Moderate	0	0	8	5	0	0	0	2
Marked	0	0	6	3	0	0	13	11

[a] = Number of tissues examined from each group

Table 3.9.2-3 (taken directly from the study report) provides a summary of the test article-related histologic findings in the skin, both untreated control skin and application site, at scheduled termination.

Skin (untreated control skin): Atrophy of the epidermis, dermis and adnexa and variable hyperkeratosis were generally observed in untreated control skin from most animals at ≥0.05% HBP. Telogen hair follicles, often containing no hair shafts, were frequent and were often accompanied by variable follicular atrophy. Variable atrophy of the sebaceous gland was also observed routinely.

Skin (application site): Almost all morphologic features observed in untreated control skin were also evident in skin from the application site, with the notable exception of epidermal atrophy. In contrast to untreated control skin, slight to marked hyperplasia of the epidermis was observed at the application site in most animals, except in sham controls.

Text Table 3.9.2-3: Incidence and Severity of Selected Test Article-Related Histopathologic Findings in the Skin-Terminal Sacrifice

Group/sex	1M	2M	3M	4M	1F	2F	3F	4F
Halobetasol Propionate Conc. (%)	**0**	**0**	**0.05**	**0.1**	**0**	**0**	**0.05**	**0.1**
Topical Application Site (AS) [a]	15	14	14	8	15	15	14	13
Atrophy, Hair Follicles								
Minimal	0	0	1	0	0	0	0	0
Moderate	0	0	1	0	0	0	0	0
Marked	0	0	10	7	0	0	11	11
Severe	0	0	2	1	0	0	3	2
Atrophy, Glands								
Slight	0	0	3	1	0	0	1	1
Moderate	0	0	2	1	0	0	3	7
Marked	0	0	1	2	0	0	0	1
Severe	0	0	0	1	0	0	0	0
Atrophy, Dermis								
Slight	0	0	9	0	0	0	6	5
Moderate	0	0	2	7	0	0	5	1
Marked	0	0	1	1	0	0	0	0
Hyperplasia, Epidermal								
Minimal	0	0	0	0	1	1	0	1
Moderate	0	8	1	0	1	4	1	3
Slight	0	4	11	7	0	9	10	6
Marked	0	1	1	1	0	0	3	3
Topical AS, Untreated Control [a, b]	15	14	13	8	15	15	13	13
Atrophy, Hair Follicles								
Slight	0	0	1	0	0	0	1	2
Moderate	0	0	12	4	0	0	10	9
Marked	0	0	0	4	0	0	2	2
Atrophy, Dermis								
Slight	0	0	3	1	0	0	3	5
Moderate	0	0	8	5	0	0	3	3
Marked	0	0	2	2	0	0	0	0
Atrophy, Glands								
Slight	0	0	5	1	0	0	1	4
Moderate	0	0	6	4	0	0	10	3
Marked	0	0	0	2	0	0	1	3
Atrophy, Epidermal								
Slight	0	0	4	5	0	0	8	7
Moderate	0	0	5	2	0	0	3	1
Marked	0	0	1	0	0	0	0	0

[a] = Number of tissues examined from each group
[b] = Skin collected from cervical dorsal region; no treatment with the test article or vehicle occurred at this site.

Test article-related secondary findings were largely the result of immunosuppression (evidenced by lower lymphoid organ weights, lymphopenia, decreased globulin, etc.) attributable to the systemic absorption of HBP. Most of these findings were the result of opportunistic bacterial infections and were generally similar to those observed in unscheduled decedents (*e.g.*, inflammation in lungs, pyelonephritis, etc.) albeit at generally lower severity. The high

incidence of ulceration/inflammation/abscesses in the extremities of HBP-treated rats may be related in part to impaired wound healing which is a known effect of glucocorticoids (Schacke *et al*., 2002).

Toxicokinetics

On days 1 and 90 blood samples were obtained for toxicokinetic determinations from up to 3 animals/sex/time point from Groups 3 and 4 predose and 0.5, 1, 2, 4, 8, and 24 hours post-dose. Blood samples were collected on days 1 and 90 from 3 animals/sex from Group 2 at 2 hours post-dose.

The values for C_{max} and AUC_{0-t} were higher for the 0.1% lotion than for the 0.05% lotion for both males and females on both Day 1 and Day 90. The increases in exposure were approximately linear with concentration for males, but were less than proportional to concentration for females. There was an increase in systemic exposure, as measured by C_{max} and AUC_{0-t} with multiple dosing for both males and females. With the exception of a T_{max} value of 4 hours for females in Group 4 on day 1, T_{max} occurred at 1 or 2 hours post-application for all other sex/dose/day groups indicating rapid absorption of HBP from the lotion. The half-life for elimination of HBP after topical application ranged from 4.51 to 17.6 hours, with longer $t_{1/2}$ values associated with the higher dose level. C_{max} and AUC_{0-t} were higher for females than males indicating a gender difference in the extent of systemic exposure. There was no apparent gender difference in T_{max} at either dose level or in $t_{1/2}$ at the lower dose level.

Table 3. Values for Pharmacokinetic Parameters for Halobetasol Propionate

Group	Lotion Concentration	Sex	Day	C_{max} (pg/mL)	T_{max} (hr)	AUC_{0-t} (pg•hr/mL)	$t_{1/2}$ (hr)
3	0.05%	M	1	2,602	2	22,053	7.43
			90	6,775	2	49,143	6.67
			% Difference	160%		123%	
3	0.05%	F	1	8,285	1	82,668	4.51
			90	16,132	2	119,711	8.31
			% Difference	95%		45%	
4	0.1%	M	1	4,192	2	39,396	9.59
			90	15,572	1	116,165	8.57
			% Difference	271%		195%	
4	0.1%	F	1	11,644	4	111,999	nc
			90	19,906	2	167,888	17.6
			% Difference	71%		50%	

nc = could not be calculated by WinNonlin.

Dosing Solution Analysis

No analyses were performed for this study. Test articles were administered as provided and verified by CoA (Annex 1).

Pharmacology/Toxicology discussion:
Data from the 13-week dermal study showed that HBP Lotion 0.05% and 0.1% caused marked immunosuppression in animals resulting in the development of opportunistic infections as well as significant toxicity in multiple organ systems after receiving only 13 weeks of daily dermal dosing. Due to anticipated survivability and general health concerns, it will not be possible to conduct a 2-year dermal carcinogenicity study on this drug product. Accordingly, the sponsor is granted a waiver for the conduct of the 2-year dermal carcinogenicity study.

Comments to be relayed to the sponsor:

A waiver request is granted for conduct of the 2-year dermal carcinogenicity study for Halobetasol Propionate Lotion, 0.05% based on the severe immunosuppression noted in the 13 week dermal toxicity study in rats.

References

Schacke H, Docke WD, Asadullah K. 2002. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther 96:23-43.

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/s/

JILL C MERRILL
08/08/2014

BARBARA A HILL
08/08/2014

Memorandum

To: IND (b) (4)
From: Jill C Merrill
Re:
SDN: 15, 27
Date: 12-22-2010, 12-08-2011

Type: nonclinical information
Drug: Halobetasol Propionate Lotion, 0.05%
Sponsor: (b) (4)
Indication: moderate to severe plaque psoriasis

Information to sponsor: no

Review date: 10-02-13

Background:

The sponsor submitted an IND for a potential 505(b)2 approval of a novel formulation containing 0.05% halobetasol propionate (HBP) for the topical treatment of moderate to severe plaque psoriasis (11-23-2008). The active ingredient is well characterized and the concentration is known to be safe and effective as a topical anti-inflammatory and antipruritic agent in different formulations approved by the FDA. The sponsor was informed (12-19-2008) that given the long history of safe use of multiple HBP formulations and assuming an adequate clinical bridge could be established to a previously approved HBP formulation (i.e., Ultravate® Cream, NDA 19967) it was acceptable to use the Agency's findings of safety to support the systemic safety of their topical formulation and use the 505(b)2 regulatory approval pathway.

The topical formulation to be investigated in the Phase 3 clinical study is formulation R9860 (Table 5, taken directly from the sponsor's End-of-Phase 2 briefing package).

Table 5. Composition and Batch Formula for Halobetasol Propionate Lotion, 0.05% (Formulation R9860)

Ingredient	Purpose	Composition (% w/w)	Quantity (kg)
Diisopropyl Adipate	[redacted]		
Octyldodecanol, NF			
Ceteth 20 [redacted]			
Poloxamer 407, NF			
Cetyl Alcohol, NF			
Stearyl Alcohol, NF			
Propylparaben, NF			
Butylparaben, NF			
Glycerin, USP			
Carbomer Homopolymer, NF			
Propylene Glycol, USP			
Sodium Hydroxide, NF [redacted]			
Halobetasol Propionate	Active	0.05	0.05
[redacted] Water, USP	[redacted]		
Total			100.00

[redacted]

Information contained in SDN 15:

The sponsor has submitted a final study report for the primary eye irritation study conducted in rabbits (Study # 0421LT28.002) with a HBP lotion 0.05% (formulation # PD09015, formerly known as R9861). The final study report does not differ substantially from the previously reviewed draft report (reviewed by Dr. Jill Merrill under IND [redacted], SDN 6, entered in DARRTS 11-1-2012). The formulation was found to be slightly irritating in rabbits.

The sponsor has submitted a final study report for the 28-day repeat dose dermal toxicity study conducted in minipigs with HBP lotion at 0.05% and 0.1% (Study # 1246-007). The final study report does not differ substantially from the previously reviewed draft report (reviewed by Dr. Jill Merrill under IND [redacted], SDN 10, entered in DARRTS 11-1-2012). The results from this study were consistent with the known pharmacological activities and toxicological effects of corticosteroids.

Information contained in SDN 27:

The sponsor has submitted a study report (MC11M-0013) profiling the metabolites of HBP generated by commercially available cryopreserved human hepatocytes ([redacted]). Consumption of HBP (1.0 µM) in

the hepatocyte incubations resulted in 7.99% of parent compound remaining after 120 minutes. A control incubation in pure medium showed no loss of HBP in the absence of hepatocytes, indicating all parent consumption was enzyme-dependent. At a concentration of 1.0 µM, HBP was consumed in incubations using human hepatocytes in a log-linear fashion with a half-life value of 33 minutes.

Following incubation of HBP at 15.0 µM with human hepatocytes, a total of ten potential metabolites were observed. Tentatively characterized metabolites include desaturation of the parent compound (M6), hydroxylation (M8 and M9), and dehalogenation in combination with several of these transformations. Both dechlorination (M3 and M11) and defluorination (M4, M5, and M7) were observed, with one metabolite being formed by both dechlorination and defluorination (M2).

The most predominant metabolite based upon extracted ion chromatogram peak heights was M8. Two other metabolites with notable abundance were M5 and M7. The remaining metabolites were detected at very low levels.

Pharmacology/Toxicology discussion:

The sponsor has submitted final study reports for an acute eye irritation study and a 28-day repeat dose dermal toxicity study conducted in minipigs. The final study reports are not substantially different from the draft reports, both of which have been previously reviewed (entered in DARRTS 11-1-2012). In addition the sponsor has submitted a study report for an *in vitro* study profiling the metabolites generated by human hepatocytes incubated with HBP.

As per the End-of-Phase 2 meeting (07-25-2012), the sponsor is planning a 13-week dermal range finding study in rats to determine the feasibility of a potential 2-year dermal carcinogenicity study.

Comments to be relayed to the sponsor:

None at this time.

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/s/

JILL C MERRILL
10/02/2013

BARBARA A HILL
10/02/2013

Memorandum

To: IND (b) (4)
From: Jill C Merrill
Re:
SDN: 35
Date: 10-26-12

Type: Clinical SPA
Drug: Halobetasol Propionate Lotion, 0.05%
Sponsor: (b) (4)
Indication: moderate to severe plaque psoriasis

Information to sponsor: no

Review date: 11-07-12

Background:

The sponsor submitted an IND for a potential 505(b)(2) approval of a novel formulation containing 0.05% halobetasol propionate (HBP) for the topical treatment of moderate to severe plaque psoriasis (11-23-2008). The active ingredient is well characterized and the concentration is known to be safe and effective as a topical anti-inflammatory and antipruritic agent in different formulations approved by the FDA. The sponsor was informed (12-19-2008) that given the long history of safe use of multiple HBP formulations and assuming an adequate clinical bridge could be established to a previously approved HBP formulation (i.e., Ultravate® Cream, NDA 19967) it was acceptable to use the Agency's findings of safety to support the systemic safety of their topical formulation and use the 505(b)(2) regulatory approval pathway.

Information contained in SDN35:

The sponsor proposes a Phase 3 study entitled: A multicenter, randomized, double-blind, parallel group comparison of Halobetasol Propionate Lotion 0.05% versus Vehicle Lotion in subjects with plaque psoriasis (Protocol # 000-0551-304). The primary objective is to determine and compare the efficacy and safety of HBP Lotion 0.05% (formulation R9860) and the Vehicle Lotion applied twice daily for two weeks. This protocol is the second of two clinical studies designed to support an eventual NDA for IND (b) (4) Protocol 304 is similar in design, endpoints, efficacy and safety assessments to Protocol 305 (SDN34) except that Protocol 304 is a 2-arm study, comparing the drug product and its vehicle, whereas Protocol 305 is a 4-arm study including the Listed Drug, Ultravate Cream, 0.05% and placebo cream.

Pharmacology/Toxicology discussion:

The clinical protocol proposes a maximum dermal dose of 0.818 µg/cm^2 HBP for 14 days (1.8 mg of HBP (3.6 g HBP lotion x 0.05% HBP) per 2200 cm^2). The same HBP formulation was tested in the 28-day repeat dermal dose minipig study (Study # 1246-007; SDN10; reviewed/entered in DARRTS 11-1-2012). The clinical observations and toxicities noted in this nonclinical study were consistent with the known effects of corticosteroids. The nonclinical study supports the use of this HBP formulation and the proposed clinical Protocol 304 incorporates the appropriate safety parameters.

Comments to be relayed to the sponsor: None.

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/s/

JILL C MERRILL
11/07/2012

BARBARA A HILL
11/07/2012

Memorandum

To: IND (b) (4)
From: Jill C Merrill
Re:
SDN: 6, 10, 34
Date: 1-25-10, 6-30-10, 10-22-12

Type: nonclinical information; Clinical SPA
Drug: Halobetasol Propionate Lotion, 0.05%
Sponsor: (b) (4)
Indication: moderate to severe plaque psoriasis

Information to sponsor: no

Review date: 10-31-12

Background:

The sponsor submitted an IND for a potential 505(b)2 approval of a novel formulation containing 0.05% halobetasol propionate (HBP) for the topical treatment of moderate to severe plaque psoriasis (11-23-2008). The active ingredient is well characterized and the concentration is known to be safe and effective as a topical anti-inflammatory and antipruritic agent in different formulations approved by the FDA. The sponsor was informed (12-19-2008) that given the long history of safe use of multiple HBP formulations and assuming an adequate clinical bridge could be established to a previously approved HBP formulation (i.e., Ultravate® Cream, NDA 19967) it was acceptable to use the Agency's findings of safety to support the systemic safety of their topical formulation and use the 505(b)2 regulatory approval pathway.

The topical formulation to be investigated in the Phase 3 clinical study is formulation R9860 (Table 5, taken directly from the sponsor's end of phase 2 briefing package).

Table 5. Composition and Batch Formula for Halobetasol Propionate Lotion, 0.05% (Formulation R9860)

Ingredient	Purpose	Composition (% w/w)	Quantity (kg)
Diisopropyl Adipate	[redacted]		
Octyldodecanol, NF			
Ceteth 20 [redacted]			
Poloxamer 407, NF			
Cetyl Alcohol, NF			
Stearyl Alcohol, NF			
Propylparaben, NF			
Butylparaben, NF			
Glycerin, USP			
Carbomer Homopolymer, NF			
Propylene Glycol, USP			
Sodium Hydroxide, NF [redacted]	[redacted]		
Halobetasol Propionate	Active	0.05	0.05
[redacted] Water, USP	[redacted]		
Total			100.00

* [redacted]

Information contained in SDN6:

The sponsor has performed a primary eye irritation study in rabbits (Study # 0421LT28.002). Under the conditions of this study Halobetasol Propionate Lotion 0.05% (formulation # PD09015, formerly known as R9861) was not considered to be an ocular irritant. The same HBP lotion 0.05% formulation was not considered to be a skin sensitizer when tested in a Buehler sensitization test (Study # 09-2195-G2). In a 28-day toxicokinetic study in minipigs (Study # 1246-006), twice daily treatment with HBP lotion 0.05% (R9861) or an enhanced formulation containing 0.1% HBP (R9874) were tested. The findings from this study were consistent with the known pharmacological activities and toxicological effects of corticosteroids.

Recent data have indicated that the R9861 formulation is not optimal. The sponsor is transitioning to formulation R9860, which is identical to R9861 with respect to inactive ingredients and percentages with the exception of the addition of [redacted] propylene glycol.

Information contained in SDN10:

6.2 Repeat-Dose Toxicity

Study title: Halobetasol Propionate Lotion: A 4-week dermal toxicity study in Gottingen minipigs

Study no.:	1246-007
Study report location:	SDN10
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Feb 18, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	HBP Lotion vehicle, PD09042, not provided 0.05% HBP Lotion, PD09044, 99.4% 0.10% HBP Lotion, PD09043, 100.4%

Key Study Findings

Twice daily topical administration of HBP lotion at concentrations of 0.05% and 0.1% for 28 days in minipigs produced: adrenal gland atrophy, bone marrow hypocellularity, and minimal to severe generalized lymphoid depletion in lymph nodes, GALT, spleen, and thymus gland. A decrease in reticulocytes was also observed that was associated with the bone marrow hypocellularity observed microscopically.

Based on these data, halobetasol propionate lotion at concentrations of 0.05% (the clinical concentration) and 0.10% did not produce any new or unique toxicity that has not been previously observed with corticosteroid drugs.

Methods

Doses:	0 (untreated control), 0% (vehicle control), 0.05%, 0.10% HBP lotion Daily dose: 0, 0, 0.15, 0.30 mg/kg
Frequency of dosing:	Twice daily (~8 hours apart)*
Route of administration:	Dermal to clipped dorsal surface ≥ 10% BSA
Dose volume:	4 mg/cm^2 (based on density measurement of 0.977 g/mL)
Formulation/Vehicle:	Clinical formulation and enhanced
Species/Strain:	Gottingen Minipigs
Number/Sex/Group:	4
Age:	~4-5 months of age
Weight:	Males: 8.6 - 13.1 kg; Females: 9.65 – 13.05 kg
Satellite groups:	no
Unique study design:	Only 2 dose levels, as previously agreed with DDDP
Deviation from study protocol:	None significant to the integrity of the study

*Applications of lotion were not occluded and any residual lotion from the previous dose was removed using tepid water and a paper towel.

Calculations:

0.1% HBP = 1 mg/mL
Density of lotion = 0.977 g/mL
2 mL x 0.977 g/mL = 1.954 g lotion
4 mg/cm^2 x 480 cm^2 = 1920 mg lotion
1.920 g lotion x 0.1% HBP = 1.92 mg HBP
1.92 mg / 12.5 kg = 0.1536 mg/kg (systemic dose HBP)
1.92 mg ÷ 480 cm^2 = 4 µg/cm^2 (dermal dose HBP)
HED 0.1536 mg/kg x 35 = 5.376 mg/m^2
HED 0.1536 mg/kg x 35/37 = 0.145 mg/kg

2 x (0.1% HBP lotion x 4 mg/cm^2 x 480 cm^2) ÷ 12.5 kg
= 2 x 1.92 mg ÷ 12.5 kg
= 0.30 mg/kg

Observations and Results

Mortality

All animals were observed for morbidity, mortality, injury and availability of feed and water twice daily throughout the study. All animals survived to scheduled necropsy on Day 29.

Clinical Signs

Detailed clinical examinations were performed prior to randomization and weekly during the study. The observations included evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling and bizarre behavior.

Skin of the test site was scored for erythema/eschar and edema once prior to initial dosing and once daily (prior to second daily dosing) for changes in application site based upon the Draize scale for scoring skin reactions.

No test article-related clinical findings were observed in any of the minipigs during the 4-week study. Some of the findings noted (scabbed areas, abrasions, brown, blue or red discolored skin and material around the eyes) are commonly seen in Gottingen Minipigs under laboratory conditions.

The incidence of erythema was less in Halobetasol Propionate Lotion 0.05% and 0.1% groups than the vehicle control in both males and females.

The incidence of edema was less in Halobetasol Propionate Lotion 0.05% and 0.1% groups than the vehicle control in both males and females.

Body Weights

Body weights were recorded the day after receipt, prior to randomization (Day -1) and weekly during the study.

The mean body weights for males did not show a significant gain at 0.05% and were decreased by 2.4% from pretest at 0.1%, while mean body weight in both groups of treated females decreased by 4.0% and 3.8% from pretest at 0.05% and 0.1%, respectively (see text table below entitled Body Weights, taken directly from the study report). These changes in body weights are minor and not considered to be toxicologically significant.

Reviewer's comment: Percent difference in the following table is incorrectly listed as percent difference from control. It should be described as relative to pretest values.

Body Weights, kg						
	Male			Female		
Dose Concentration	Pretest	Week 4	(%)	Pretest	Week 4	(%)
Untreated Control	11.31	12.81	(+13.3)	10.76	12.40	(+15.2)
Placebo Control	10.35	11.83	(+14.3)	11.21	12.89	(+15.0)
0.05%	10.98	11.05	(+0.6)	11.86	11.38	(-4.0)
0.1%	10.89	10.63	(-2.4)	10.50	10.10	(-3.8)
(%) – Percent difference from control						

Feed Consumption

Not measured.

Ophthalmoscopy

Ophthalmoscopic examinations were conducted on all animals pretest and prior to scheduled termination. No test article-related ophthalmic abnormalities were detected during examination either at pretest or terminal examination. At the terminal examination retinitis was observed in the left eye of one female treated with 0.1% HBP Lotion, but this was considered to be within the limits of variation commonly seen in the species.

ECG

All animals received an ECG examination during the last week of dosing (predose and 1-2 hours post the first daily dose). Standard ECGs (6 lead) were recorded at 50 mm/sec. Using an appropriate lead recorded at 50 mm/sec, the RR, PR, and QT intervals and QRS duration were measured and heart rate was determined. Corrected QT (QTc) interval was calculated using a procedure based on the method described by Fridericia.

The dermal administration of HBP Lotion did not cause any qualitative or quantitative ECG abnormalities.

Hematology

Blood samples (4.8 – 5.8 mL) were collected from the anterior vena cava from overnight fasted animals pretest and again prior to necropsy. The samples were collected into tubes containing K_3EDTA for evaluation of the following parameters: leukocyte count (total and absolute differential), erythrocyte count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated), absolute reticulocytes, platelet count, blood cell morphology. Blood samples were collected into tubes with sodium citrate for the coagulation parameters: prothrombin, and activated partial thromboplastin time.

At the terminal evaluation there were test article-related increases in neutrophils with concurrent decreases in lymphocytes and eosinophils at the 0.05% and

0.1% concentrations in both sexes (see text table below entitled Summary of Effects on Hematology Parameters, taken directly from the study report). Overall, these changes resulted in minimal to mild increases in total leukocytes at the 0.1% concentration in both males and females and in males only at 0.05%. In addition, there were moderate to marked test article-related decreases in reticulocytes in both sexes at both concentrations that did not follow a consistent dose response. These changes are indicative of suppression of red cell production and are consistent with the minimal bone marrow hypocellularity observed microscopically.

All other hematology values in the treated groups were comparable to controls. No test article-related coagulation alterations were seen in males or females at the terminal evaluation.

Summary of Effects on Hematology Parameters[a]

Dose Concentration	0.05%		0.1%	
	Male	Female	Male	Female
Leukocytes	↑33	↓7	↑33	↑141[b]
Neutrophils	↑162[b]	↑198[b]	↑187[b]	↑724[b]
Lymphocytes	↓41	↓67[b]	↓61[b]	↓33
Eosinophils	↓77[b]	↓81[b]	↓79[b]	↓76
Basophils	↓44	↓44	↓44	↓17
Other Cells	↓6	↓22	↑24	↑131
Reticulocytes	↓87	↓66	↓86	↓61

[a]Change relative to untreated controls
[b]Statistically significant
↑↓: percent change

Clinical Chemistry

Blood samples (4.8 – 5.8 mL) were collected from the anterior vena cava from overnight fasted animals pretest and again prior to necropsy. The samples were collected into tubes without anticoagulant for evaluation of the following parameters: alkaline phosphatase, total bilirubin, aspartate aminotransferase, alanine aminotransferse, gamma glutamyl transferase, sorbitol dehydrogenase, urea nitrogen, creatinine, total protein, albumin, globulin and A/G (albumin/globulin ratio; calculated), glucose, total cholesterol, triglycerides, electrolytes (sodium, potassium, chloride) calcium, phosphorus.

There were mild decreases in chloride, creatinine, A/G ratio, triglyceride, and alkaline phosphatase with concurrent increases in urea nitrogen, cholesterol, and globulin in both sexes at the terminal evaluation (see text table below entitled Summary of Effects on Clinical Chemistry Parameters, taken directly from the

study report). These test article-related changes did not follow a dose response and were not considered to be biologically relevant at the observed magnitudes.

Summary of Effects on Clinical Chemistry Parameters[a]

Dose Concentration	0.05%		0.1%	
	Male	Female	Male	Female
Chloride	↓6[b]	↓3	↓6[b]	↓5[b]
Urea Nitrogen	↑63[b]	↑112[b]	↑83[b]	↑107[b]
Creatinine	↓42[b]	↓29[b]	↓27[b]	↓42[b]
Globulin	↑19	↑23	↑36[b]	↑23
A/G Ratio	↓18	↓17	↓28	↓25
Cholesterol	↑98[b]	↑22	↑89[b]	↑32[b]
Triglyceride	↓46[b]	↓23	↓42[b]	↓15
Alkaline Phosphatase	↓46[b]	↓79[b]	↓61[b]	↓59[b]

[a]Change relative to untreated controls
[b]Statistically significant
↑↓: percent change

Urinalysis

Not performed.

Gross Pathology

Animals were euthanized by an intravenous overdose of sodium pentobarbital under Telazol sedation followed by exsanguination via severing the femoral vessels. The animals were examined for external abnormalities including masses. The skin was reflected from a ventral midline incision and any abnormalities were identified and correlated with antemortem findings. The thoracic, abdominal, and cranial cavities were examined for abnormalities and the organs removed, examined and where required placed in fixative. All designated tissues were fixed in neutral buffered formalin, except for the eye (including the optic nerve) and testes, which were fixed using a modified Davidson's fixative. Formalin was infused into the lungs.

Halobetasol propionate lotion-related macroscopic effects were limited to mildly small adrenal glands in one of four 0.1% males and moderately small thymus glands in one of four females in both the 0.05% and 0.1% groups. Small adrenal gland size correlated with microscopic adrenal cortical atrophy and reduced adrenal gland weights. Small thymus gland size correlated with generalized thymic lymphoid depletion and decreased thymus gland weights.

Organ Weights

Organ weights were recorded for all animals at scheduled necropsy and appropriate organ weight ratios were calculated (relative to body and brain

weights) for the following organs: adrenal gland, brain (cerebrum, midbrain, cerebellum, medulla/pons), epididymis, heart, kidney, liver, lung with bronchi, ovary, pituitary, salivary gland (mandibular), spleen, testis, thymus, thyroid gland.

Halobetasol propionate lotion-related organ weight changes were observed in males and females at 0.05% and 0.1% and consisted of decreased absolute and relative adrenal gland, spleen, thymus gland and testes weights and increased absolute and relative liver weights (see text table below entitled Test Article-related Organ Weight Changes - Terminal, taken directly from the study report). The magnitude of change was often similar between the 0.05% and 0.1% groups. Decreased adrenal gland weights correlated with microscopic adrenal cortical atrophy. Decreased spleen and thymus gland weights correlated with microscopic generalized lymphoid depletion. Although increased splenic weights were observed in 0.05% females, lymphoid depletion was observed microscopically; splenic weights can be highly variable dependent on the degree of blood congestion at euthanasia. Decreased testicular weights correlated with seminiferous tubule degeneration/atrophy. Increased liver weights correlated with microscopic panlobular hepatocellular hypertrophy

All other organ weight changes were considered incidental and reflective of expected biological variation based on lack of microscopic correlates.

Test Article-related Organ Weight Changes - Terminal Male and Female (Percent change relative to control)				
Dose concentration: %	0.05		0.1	
Sex	M	F	M	F
Number Examined	4	4	4	4
Adrenal Glands	↓42.4[b]	↓35.2[b]	↓40.6[b]	↓37.1[b]
Adrenal Glands /BWt%	↓30.9[a]	↓29.8[b]	↓26.4	↓23.1[a]
Adrenal Glands /BrWt ratio	↓39.2[b]	↓31.2[b]	↓36.2[b]	↓33.5[b]
Liver	↑7.5	↑25.6[b]	↑14.8	↑17.4[a]
Liver /BWt%	↑26.0[b]	↑35.1[b]	↑39.7[b]	↑45.1[b]
Liver /BrWt ratio	↑12.6	↑33.0[b]	↑23.8	↑25.6[a]
Spleen	↓39.8	↑19.1	↓67.0[a]	↓42.5
Spleen /BWt%	↓29.8	↑28.1	↓59.1[a]	↓30.3
Spleen /BrWt ratio	↓37.5	↑23.9	↓64.0[a]	↓40.6
Thymus	↓55.9[a]	↓35.4	↓50.5	↓54.9
Thymus /BWt%	↓50.1[a]	↓30.7	↓41.0	↓46.1
Thymus /BrWt ratio	↓53.0[a]	↓30.3	↓46.2	↓52.6
Testes	↓25.0[a]	NA	↓32.1[a]	NA
Testes /BWt%	↓12.2	NA	↓18.3	NA
Testes /BrWt ratio	↓20.3	NA	↓26.5	NA

[a]Significantly different from untreated control; ($p<0.05$) ↑ - Increased
[b]Significantly different from untreated control; ($p<0.01$) ↓ - Decreased
NA – Not Applicable/Not Available M – Male
BWt - Body Weight F - Female
BrWt - Brain Weight

Histopathology

Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections was performed on the following tissues from all animals: adrenal gland, aorta, bone with bone marrow (femur), bone with bone marrow (rib), bone with bone marrow (sternum), bone marrow smear, brain (cerebrum, midbrain, cerebellum, medulla/pons) epididymis, esophagus, eye (with optic nerve), gallbladder, gut associated lymphoid tissue (GALT), heart, joint (tibiofemoral), kidney, large intestine (cecum), large intestine (colon), large intestine (rectum), larynx, liver, lung with bronchi, lymph node (mandibular), lymph node (mesenteric), mammary gland (process in females only), nerve (sciatic), ovary, oviducts, pancreas, pituitary, prostate, salivary gland (mandibular), salivary gland (parotid), salivary gland (sublingual), seminal vesicle, skeletal muscle, skin (treated and untreated), small intestine (duodenum), small intestine (ileum), small intestine (jejunum), spinal cord (cervical), spinal cord (lumbar), spinal cord (thoracic), spleen, stomach (cardia), stomach (non-glandular), stomach (fundus), stomach (pylorus), testis, thymus, thyroid gland, tongue, trachea, ureters, urinary bladder, uterus with cervix, vagina, gross lesions, tissue masses with regional lymph node.

Adequate Battery -yes

Peer Review – none noted.

Histological Findings

Halobetasol propionate-related microscopic effects were observed in the adrenal glands, lymphoid system (including lymph nodes, spleen, and thymus gland); bone (rib, femur, tibia, and sternum) and bone marrow (rib and sternum); liver; kidneys; skin; stomach (esophageal region) and testes. Changes were noted in most animals in both HBP groups and were similar in severity.

Minimal to mild adrenal cortical atrophy was observed in all males and females treated with HBP lotion at 0.05% and 0.1%. This finding was characterized by a diffuse generalized thinning of the adrenal cortex with reduction in cell size with/without cellular loss.

Generalized lymphoid depletion was observed in the thymus gland, spleen, and lymph nodes (mesenteric, mandibular and/or GALT) and was characterized by an absolute or relative reduction in the number of lymphocytes in all lymphoid compartments. The severity was minimal to mild in all organs (moderate only for mesenteric lymph nodes in the females) except the thymus where it ranged from mild to severe.

Bone marrow hypocellularity (minimal) was characterized by an absolute reduction in bone marrow cells from all lineages (erythroid, myeloid, lymphoid, and megakaryocytes).

Panlobular hepatocellular hypertrophy (minimal to mild) was characterized by a generalized enlargement of hepatocytes.

Minimal renal tubular degeneration was characterized by degeneration (cellular swelling and/or shrinkage with nuclear alterations) of scattered individual tubular epithelial cells. In addition, one 0.1% male had presence of tubular casts characterized by granular or cellular debris accumulations within the tubules.

Skin atrophy (minimal) was observed in both treated and untreated skin regions and was characterized by a diffuse, generalized thinning of the epidermis.

Testicular seminiferous tubular degeneration/atrophy (minimal) was characterized by focal reduction of cellularity, loss of spermatogenesis, cytoplasmic vacuolation of sustentacular cells, formation of multinucleated syncytial or giant cells, loss of cell layers, and/or intraluminal cellular debris within seminiferous tubules.

Special Evaluation

Not performed.

Toxicokinetics

Blood samples (~ 2 mL) were collected from all animals via the anterior vena cava for determination of plasma concentrations predose and ~1, 2, 4, 8, 9, 10, 14, and 24 hours after the first daily dose on Days 1 and 28. Samples were collected in tubes containing K_3EDTA anticoagulant and processed to plasma and shipped on dry ice to Ricerca Bioscience, for analysis of plasma concentrations of the test article.

None of the animals in the untreated control group or vehicle control group had any measurable concentrations of HBP. There were no measurable plasma concentrations of HBP on Day 1. On day 28, C_{max}, AUC_{0-24}, AUC_{0-8}, and AUC_{8-24} were higher for males and females receiving 0.1% HBP lotion than for males and females receiving 0.05% HBP Lotion (see Table 2, Figure 1, taken directly from the study report). There was no evidence of a gender difference.

Table 2. Mean Pharmacokinetic Parameters for Halobetasol Propionate on Day 28

Parameter	Sex	Group	Treatment	Mean ± SD	Median	Range
C_{max} (ng/mL)	M	3	0.05%	0.340 ± 0.405	0.278	0 - 0.804
		4	0.10%	0.815 ± 0.238	0.713	0.663 - 1.17
	F	3	0.05%	0.287 ± 0.333	0.271	0 - 0.607
		4	0.10%	1.01 ± 0.14	1.08	0.803 - 1.09
T_{max} (hr)	M	3	0.05%	9.00 [a]	9.00	9 - 9
		4	0.10%	3.75 ± 5.56	1.50	0 - 12
	F	3	0.05%	6.00 [a]	6.00	2 - 10
		4	0.10%	7.25 ± 4.19	9.00	1 - 10
AUC_{0-24} (ng•hr/mL)	M	3	0.05%	5.45 ± 7.27	3.20	0 - 15.4
		4	0.10%	14.3 ± 2.31	15.0	11.0 - 16.3
	F	3	0.05%	3.66 ± 6.31	0.796	0 - 13.1
		4	0.10%	15.4 ± 7.12	15.5	6.57 - 23.9
AUC_{0-8} (ng•hr/mL)	M	3	0.05%	1.69 ± 2.58	0.660	0 - 5.45
		4	0.10%	5.27 ± 0.76	4.95	4.79 - 6.38
	F	3	0.05%	1.42 ± 2.18	0.536	0 - 4.61
		4	0.10%	5.65 ± 1.89	5.06	4.11 - 8.36
AUC_{8-24} (ng•hr/mL)	M	3	0.05%	3.75 ± 4.76	2.54	0 - 9.92
		4	0.10%	9.05 ± 1.89	9.98	6.21 - 10.0
	F	3	0.05%	2.24 ± 4.15	0.260	0 - 8.45
		4	0.10%	9.70 ± 5.67	10.7	1.94 - 15.5

n = 4, except as noted. Standard deviation values were not calculated when n < 3.

[a] n = 2

Information contained in SDN34:

The sponsor proposes a Phase 3 study entitled: A multicenter, randomized, double-blind, parallel group comparison of Halobetasol Propionate Lotion 0.05% versus Vehicle Lotion and an evaluator-blinded parallel group comparison of Halobetasol Propionate Lotion, 0.05% and Ultravate (halobetasol propionate) Cream 0.05% in subjects with plaque psoriasis (Protocol # 000-0551-305). The primary objective is to determine and compare the efficacy and safety of HBP Lotion 0.05% (formulation R9860) and the Vehicle Lotion applied twice daily for two weeks. The sponsor states that Ultravate Cream 0.05% is included as a comparator for safety purposes only to support generation of a clinical bridge between the novel HBP 0.05% lotion dosage form and Ultravate Cream, 0.05%. Eligible subjects will be randomized (4:4:2:1) to one of four treatment groups: HBP Lotion 0.05%; Vehicle Lotion; Ultravate Cream 0.05% or Placebo Cream. The Placebo Cream is included for blinding purposes only.

To adhere to the protocol specified dosing limitation of not more than 50 grams of test article per week, BSA involvement will be limited to 2-12% with test article applied at a rate of 1.6 mg/cm^2. The average total BSA in adults is considered 18,500 cm^2 and subjects will use 3.6 grams of test article per application (18,500 cm^2 x 12% x 1.6 mg/cm^2 = 3.6 g) for a total of 50 grams per week (3.6 g x 2 per day x 7 days = 50.4 g).

Pharmacology/Toxicology discussion:

The clinical protocol proposes a maximum dermal dose of 0.818 µg/cm^2 HBP for 14 days (1.8 mg of HBP (3.6 g HBP lotion x 0.05% HBP) per 2200 cm^2). The same HBP formulation was tested in the 28-day repeat dermal dose minipig study and the clinical observations and toxicities noted were consistent with the known effects of corticosteroids. The nonclinical study supports the use of this HBP formulation and the proposed clinical protocol incorporates the appropriate safety parameters.

Comments to be relayed to the sponsor: None.

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/s/

JILL C MERRILL
11/01/2012

BARBARA A HILL
11/01/2012

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND number: (b) (4)
Review number: 1
Sequence number/date/type of submission: 2/ 10-22-08 / original IND submission
Information to sponsor: Yes
Sponsor: (b) (4)

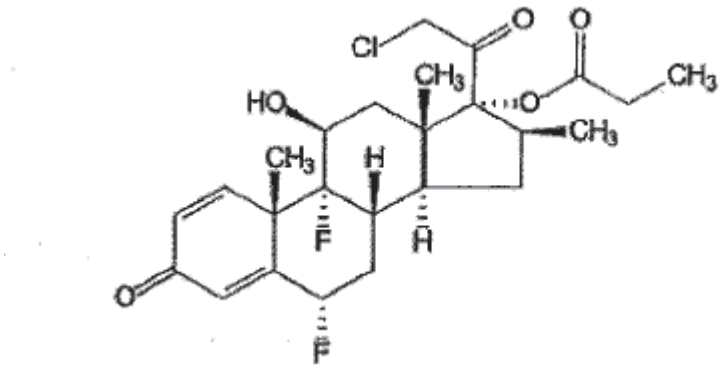
Manufacturer for drug substance: Ferndale Laboratories, Inc.
780 West Eight Mile Road
Ferndale MI 48220

Reviewer name: Jill C Merrill
Division name: Dermatology & Dental Products
HFD #: 540
Review completion date: 11-24-08

Drug:

Trade name: not provided
Generic name: halobetasol propionate lotion, 0.05%
Code name: ALC 0188, HBP
Chemical name:
21-chloro-6α, 9-difluoro-11β, 17-dihydroxy-16β- methylpregna-1, 4-diene-3-20-dione, 17-propionate
CAS registry number: 66852-54-8
Molecular formula/molecular weight: $C_{25}H_{31}ClF_2O_5$ / 485
Structure:

The structure depicted below was taken directly from the sponsor's submission.



Relevant INDs/NDAs/DMFs:

NDA 19-967, Ultravate® Cream, 0.05%

NDA 19-968, Ultravate® Ointment, 0.05%

DMF (b) (4) halobetasol propionate. The sponsor has provided a letter authorizing FDA to refer to all pages of the DMF from the holder of the DMF, Alchymars.

Drug class: superpotent topical corticosteroid

Intended clinical population: treatment of adult patients with psoriasis

Clinical formulation: The following table was taken directly from the sponsor's submission.

Component	Percent of Each Component in the Formulations					IID Level (%)
	80312-1*	80329-1	80331-1	80314-1*	80401-1	
Halobetasol propionate	0.05	0.05	0.05	0.05	0.05	--
(b) (4)						(b) (4)
Diisopropyl adipate						
Octyl-dodecanol						
Ceteth-20						
Poloxamer 407						
Oleoyl Polyoxylglycerides						
Cetyl alcohol						
Stearyl alcohol						
Propyl-paraben						
Butyl-paraben						
(b) (4)						
Propylene glycol						
Glycerin						
Carbomer (b) (4)						
(b) (4) Sodium hydroxide						
(b) (4) water						

* Formulations tested in rabbit irritation study.

(b) (4)

Each of the excipients used in the five formulations appears in the Inactive Ingredient Database (IID) at or below those specified for topical formulations except Poloxamer 407. For two of the five formulations, Poloxamer 407 is present at the (b) (4) and for the remaining three it is present at a slightly higher level (b) (4). The sponsor

also notes that a review of the IID indicates that Poloxamer 407 is also approved in a periodontal gel at (b) (4)% and that this route is sufficiently similar to the dermal route as to be applicable for topical products. In addition once a single formulation is selected for further development all of the excipients in that formulation will be qualified in a sensitization study and a repeat-dose dermal toxicology study.

All five formulations of halobetasol propionate lotion 0.05% and the placebo were dissolved in tetrahydrofuran at a concentration of 1% and scanned over the range of 200 nm to 700 nm. The original submission contains the spectra (volume 2, pages 170-175) which show no UV/VIS absorbance in the range of 290 nm to 700 nm in any of the active and placebo formulations.

Route of administration: topical

Proposed clinical protocol: The sponsor intends to conduct a phase 1 randomized, evaluator blinded, within subject, single-center evaluation of the vasoconstrictive properties of their halobetasol propionate prototype formulations in comparison to the reference drug, triamcinolone acetonide cream and vehicle lotion in healthy volunteers (n = 36) to determine potency (protocol number: 000-0551-101). Following the completion of the vasoconstriction assay study the sponsor will conduct two phase 3 efficacy studies (dosing for up to two weeks with a maximum dosage of 50 g/week) on the formulation selected for further development.

Previous clinical experience:

The sponsor intends to pursue a 505(b)2 NDA using Ultravate® Cream, 0.05% (NDA 19-967) or Ultravate® Ointment, 0.05% (NDA 19-968). No clinical studies have been conducted to date with any of the sponsor's halobetasol propionate lotion, 0.05% formulations. However, a number of studies have been completed with Ultravate® Ointment and Cream 0.05% demonstrating that halobetasol propionate is a very effective topical treatment for steroid responsive dermatoses such as psoriasis and atopic dermatitis.

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

Studies reviewed within this submission:

Primary dermal irritation study in rabbits (0420LT28.010)

Studies not reviewed within this submission: NA

TABLE OF CONTENTS

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

(b) (4) is developing Halobetasol Propionate Lotion, 0.05% for the treatment of moderate to severe plaque psoriasis. The active ingredient, halobetasol propionate is well characterized and the concentration is known to be safe and effective as an anti-inflammatory and antipruritic agent in different topical dosage formulations approved by FDA.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Like other topical corticosteroids, halobetasol propionate has anti-inflammatory, antipruritic and vasoconstrictor actions. The mechanism of the anti-inflammatory activity of topical corticosteroids 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.

Reviewer's comment: The above information was taken directly from the package insert for the reference listed drug.

2.6.2.3 Secondary pharmacodynamics

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Reviewer's comment: The above information was taken directly from the package insert for the reference listed drug.

2.6.2.4 Safety pharmacology

No safety pharmacology data in animals were located in the published literature.

2.6.2.5 Pharmacodynamic drug interactions

The sponsor has not performed any drug interaction studies nor has any information been located in the literature.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

No information on the pharmacokinetics or absorption of halobetasol propionate from the sponsor's 0.05% lotion is yet available. This will be addressed when one of the five formulations being investigated in the VCA study is selected for further development and that formulation is evaluated in the 28-day minipig study.

2.6.4.2 Methods of Analysis

The methods of analysis have not yet been developed for analyzing halobetasol propionate in minipig plasma.

Reviewer's comment: The following information on the absorption, distribution, metabolism and excretion of halobetasol propionate has been taken from the Summary Basis of Approval for Ultravate® (halobetasol propionate) Ointment, 0.05%.

2.6.4.3 Absorption

In rats, oral doses of 0.02 and 1 mg/kg tritiated halobetasol propionate resulted in absorption of 83 and 69%, respectively. Dogs dosed orally exhibited 'complete' absorption at 0.02 mg/kg and 58% absorption at 0.1 mg/kg. T_{max} in both species ranged from 3 to 4 hours. Topical administration of a 0.2% ointment resulted in 3.1% absorption in rats and 3.2 to 3.5% absorption in dogs.

2.6.4.4 Distribution

Topical application of a tritiated 0.2% halobetasol propionate ointment to rats did not produce specific accumulation in any organ or tissue.

2.6.4.5 Metabolism

Topical application of a tritiated 0.2% halobetasol propionate ointment to rats and dogs resulted in 'extensive' metabolism.

2.6.4.6 Excretion

Topical application of a tritiated 0.2% halobetasol propionate ointment to rats and dogs resulted in excretion primarily through the feces.

2.6.4.7 Pharmacokinetic drug interactions

The sponsor has not conducted any pharmacokinetic drug interaction studies on halobetasol propionate nor has any information been located in the published literature.

2.6.4.8 Other Pharmacokinetic Studies

No other pharmacokinetic studies on halobetasol propionate were located in the published literature.

2.6.4.9 Discussion and Conclusions

Information on the absorption of halobetasol propionate from the topical administration of the 0.05% lotion formulation will be developed in an upcoming 28-day minipig study prior to initiating the HPA-axis study.

2.6.4.10 Tables and figures to include comparative TK summary

Not applicable.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: Halobetasol propionate is well characterized and the concentration (0.05%) is known to be safe and effective as an anti-inflammatory and antipruritic agent in different dosage forms approved by FDA. Once a specific lotion formulation has been selected from the VCA study results, a 28-day repeat-dose dermal toxicity study will be conducted in minipigs using the selected formulation and an enhanced concentration.

Genetic toxicology: Halobetasol propionate was positive in a Chinese hamster micronucleus test and in a mouse lymphoma gene mutation assay *in vitro*. In other genotoxicity testing, halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the sister chromatid exchange test in somatic cells of the Chinese hamster, in chromosome aberration studies of germinal and somatic cells of rodents, and in a mammalian spot test to determine point mutations.

Carcinogenicity: No long-term animal studies have been performed to evaluate the carcinogenic potential of halobetasol propionate. The sponsor does not anticipate performing any carcinogenicity studies. However, given the positive findings in two genotoxicity studies (see Genetic Toxicology section above) and the anticipated chronic use of the drug product, the sponsor will be advised of the need to perform a dermal carcinogenicity study and submit the results with the NDA. The sponsor will also need to address the photocarcinogenic potential of their drug product and submit the results with the NDA.

Reproductive toxicology: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

Halobetasol propionate has been shown to be teratogenic in SPF rats and chinchilla-type rabbits when given systemically during gestation at doses of 0.04 to 0.1 mg/kg in rats and 0.01 mg/kg in rabbits. These doses are approximately 13, 33 and 3 times, respectively, the human topical dose of Halobetasol Propionate Cream, 0.05%. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats, but not in rabbits.
Studies in the rat following oral administration at dose levels up to 50 µg/kg/day indicated no impairment of fertility or general reproductive performance.

Special toxicology: Once a single formulation has been selected from the VCA study results, this formulation will be assessed in a delayed contact sensitization study in guinea pigs (Buehler) and a 28-day repeat-dose dermal toxicity study in minipigs using the selected formulation and an enhanced concentration.

2.6.6.2 Single-dose toxicity

No single dose toxicity studies were included in the current submission.

2.6.6.3 Repeat-dose toxicity

No repeat dose toxicity studies were included in the current submission.

2.6.6.4 Genetic toxicology

No genetic toxicology studies were included in the current submission.

2.6.6.5 Carcinogenicity

No carcinogenicity studies were included in the current submission.

2.6.6.6 Reproductive and developmental toxicology

No reproductive and developmental toxicology studies were included in the current IND submission.

2.6.6.7 Local tolerance

The sponsor has conducted a dermal irritation study in rabbits ((b) (4) Study # 0420LT28.010) with halobetasol propionate lotion 0.05% formulations 80312-1 and 80314-1. Each of 3 male New Zealand white rabbits received a single 0.5 mL dermal application of the lotion formulations on each of two clipped but intact skin sites per animal. Each test site was covered with a gauze patch that was held in place with a sheet of rubber dam. Exposure duration was 4 hours. Each site was evaluated for signs of dermal irritation and corrosivity immediately after patch removal and at 24, 48 and 72 hours after unwrap. Grading of the irritation was according to the method of Draize. No erythema or edema was observed at any site for any animal immediately after unwrap or

at 24, 48 or 72 hours for either test site. Based on these results halobetasol propionate lotion 0.05% (80312-1 and 80314-1) were not considered to be irritants when applied to rabbits.

2.6.6.8 Special toxicology studies

No special toxicology studies were included in the current IND submission.

2.6.6.9 Discussion and Conclusions

Results of the nonclinical dermal irritation study with two halobetasol propionate lotions 0.05% indicate that the formulations should not present a significant risk to individuals treated in the initial human VCA study. No irritation was observed. Based on this information and published data on other topical formulations containing halobetasol propionate, it is anticipated that the risk of skin irritation or sensitization with topical application of halobetasol propionate lotion 0.05% for a limited duration is minimal.

To address the need to assess repeat dose toxicity with the to-be-marketed formulation the sponsor intends to conduct a 28-day dermal toxicity study in minipigs. This duration of repeated dosing is greater than the planned clinical treatment period (14 days). Although plaque psoriasis is considered to be a chronic indication, a 9-month repeat-dose dermal toxicity study is not necessary, as the long history of topical halobetasol propionate use, as well as other potent steroids, provides information on the safety of long term use. A similar strategy has been acceptable for other topical steroids including the recent approvals of Desonate (approved 2006) and Clobex Spray (approved 2005).

2.6.6.10 Tables and Figures N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Summary: From a pharmacology/toxicology perspective, it is reasonably safe to proceed with the proposed clinical study.

Internal comments:

External comments (to sponsor):

1. If you are able to generate an adequate clinical bridge to a previously approved topical halobetasol propionate formulation (i.e., Utravate® Cream) then you can use the Agency's findings of safety to support the systemic safety of your topical halobetasol propionate formulation. If you are not able to generate an adequate clinical bridge to such a formulation, then you could obtain a right of reference

letter that would allow you to use the Agency's findings of safety for such a formulation to support the safety of your halobetasol propionate formulation. In the absence of either a clinical bridge or right of reference letter, then you would need to conduct the appropriate nonclinical toxicology studies (i.e., general toxicology, genetic toxicology, reproductive and developmental toxicology and carcinogenicity studies) to support the safety of your halobetasol propionate formulation.

2. At least 4 animals/sex/group should be used in dermal toxicology studies.

3. The potential ocular irritation of the drug product must be assessed before phase 3 clinical testing.

4. Based on the submitted absorption spectra it appears that nonclinical photosafety studies are not needed. However, you must submit a request for a waiver for nonclinical photosafety testing.

5. Psoriasis is considered a chronic indication and as per the Ultravate® label, halobetasol propionate was positive in a Chinese hamster micronucleus test. As yet no long-term animal studies have been performed to evaluate the carcinogenic potential of halobetasol propionate. Therefore, you must conduct a dermal carcinogenicity study and submit the results with the NDA. It is recommended that the protocol for the dermal carcinogenicity study be submitted to the Division to allow for evaluation by the Executive Carcinogenicity Assessment Committee of CDER (refer to the "Guidance for Industry-Carcinogenicity Study Protocol Submissions guidance document).

6. Since the photocarcinogenic potential of a formulation is independent of the UV absorption spectrum, it will be necessary to address photocarcinogenicity as per the Guidance for Industry – Photosafety Testing, and submit the results with the NDA.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Linked Applications	Sponsor Name	Drug Name
IND (b) (4)	(b) (4)	HALOBETASOLE PROPIONATE LOTION, 0.05%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JILL C MERRILL
11/24/2008

BARBARA A HILL
11/25/2008