CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-536/S-018

17-536/S-024

MEDICAL REVIEW

Medical Officer's Review of NDA 17-536

Efficacy Supplement

NDA #17-536
Serial # SE5-024/BZ
HFD#1: 006672

HFD#2: 018164

Submission date: 10/04/00
CDER Stamp date: 10/05/00
CDER Tamp date :Revised data analysis: 6/1/01
Review began: 10/10/00
Review completed: 7/17/01

Sponsor:	Schering Corporation 2000 Galloping Hill Road Kenilworth, New Jersey 07033
Generic name:	Betamethasone dipropionate
Trade name:	Diprosone Cream, 0.05%
Pharmacologic Category:	Anti-inflammatory
Indication(s):	Corticosteroid responsive dermatoses
Dosage Form(s):	Cream
Route (s) of Administration:	Topical
Related Drugs:	Diprosone Ointment – NDA 17-691 Diprosone Lotion – NDA 17-781 Diprolene AF Cream – NDA 19-555
Related Review:	Statistics draft 712/01

2 **Table of Contents**

3 Regulatory Background

This supplement is being submitted to determine the safety of use of Diprosone Cream, 0.05% in pediatric patients 12 years of age and younger.

4 Material Reviewed

NDA 19-555 SE5-024 – Volumes 1-17
NDA 19-555 SE5-024/BL – Volumes 1-8

5 Proposed Changes for Label

Note: (The 1st proposed changes for the label proposed by the sponsor (October 5, 2000) are shadowed in gray. The 2nd proposed changes that were submitted on June 1, 2001 with the reanalysis of the data are underlined.)

5.1 Proposed Clinical Pharmacology

Sixty-three pediatric patients ages 1 to 12 years, with atopic dermatitis, were enrolled in an open-label, hypothalamic-pituitary-adrenal (HPA) axis safety study. DIPROSONE Cream was applied twice daily for 2 to 3 weeks over a mean body surface area of 40% (range 35% to 90%).

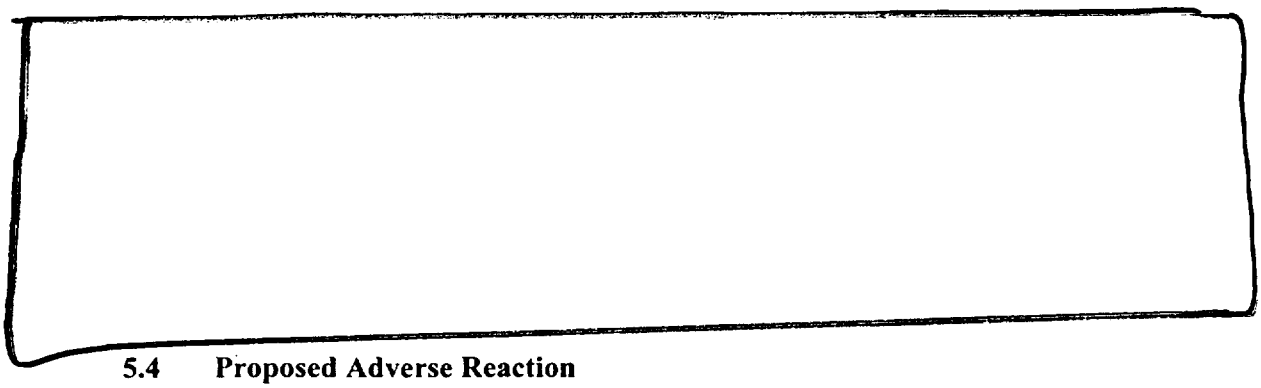
In patients, adrenal suppression was indicated by either a ≤ mcg/dL pre-stimulation cortisol, or a cosyntropin post-stimulation cortisol ≤ 18 mcg/dL and an increase of ≤ 7 mcg/dL from the baseline cortisol.

Studies performed with DIPROSONE Cream indicate that it is in the medium range of potency as compared with other topical corticosteroids.

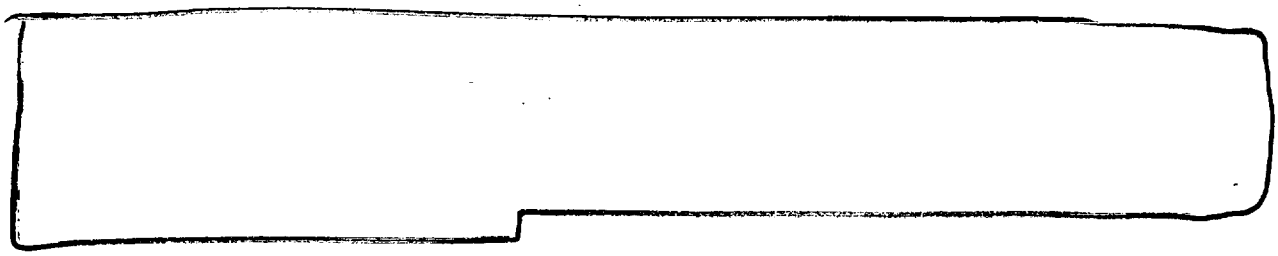
5.2 Proposed Indications and Usage

DIPROSONE Cream is a medium-potency corticosteroid[3] indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients

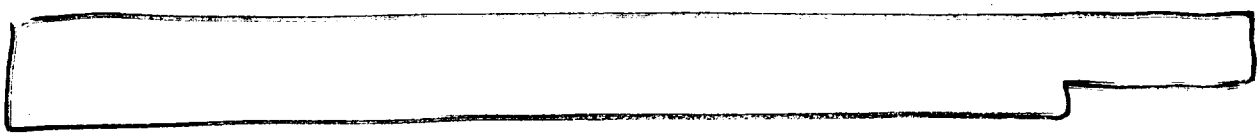
5.3 Proposed Pediatric Use



5.4 Proposed Adverse Reaction



5.5 Proposed Dosage and Administration



6 Description of Clinical Source

Study PO1262 – This is an open-label, multicenter, safety study of Diprosone Cream, 0.05% conducted in response to a pediatric written request. The study was to evaluate the systemic and cutaneous safety of Diprosone Cream, 0.05% in pediatric patients ages 3 months - 12 years of age with atopic dermatitis. The primary safety variable was the assessment of the hypothalamic-pituitary-adrenal (HPA) axis through Cortrosyn® stimulation testing. The study period was from January 17, 2000 to September 7, 2000 in which 63 subjects were enrolled. This study was aborted before the projected number of patients were enrolled because of "rate-limiting" safety. Efficacy was not requested as the efficacy of this drug product in adults can be extrapolated to pediatric patients.

7 Clinical Studies

7.1 Sponsor's protocol # - PO1262

Title: "Phase IV Multicenter, Open-Label Safety Study in Pediatric Patients with Atopic Dermatitis, Treated with Betamethasone Dipropionate, 0.05% (Diprosone Cream) Formulation"

7.11 Investigators

1. Melinda T.B. Musick, M.D.	01/Huntsville, AL
2. Thomas Horn, M.D.	02/Littlerock, AR
3. Ronald Savin, M.D.	03/New Haven, CT
4. Ivy Faaske, M.D.	04/West Palm Beach, FL
5. Craig Leonardi, M.D.	05/St. Louis, MO
6. Robert J. Kaplan, M.D.	06/Memphis, TN
7. Gloria D'Hue, M.D.	07/Atlanta, GA
8. Dow Stough, M.D.	08/Hot Springs, AR

7.1.1.1 Objective/Rationale

The objective of the study was to determine both the local and systemic safety (evaluation of HPA axis and hematology and chemistry parameters) of Diprosone Cream, 0.05% in pediatric patients 12 years of age down to 3 months of age.

7.1.1.2 Design

This was an open-label trial where patients with atopic dermatitis involving at least 35% of the body surface area were to be enrolled in a stepwise fashion beginning with 9 -12 year old patients. If no rate limiting systemic safety was observed, specifically, no suppression of the adrenals as assessed by the Cosyntropin Stimulation test, then enrollment could progress downward in a group fashion as follows: 6-8 year olds, 2-5 year olds, 3 mo. - <2 years. Rate limiting safety within any one age category group will preclude continued enrollment of subjects in the group, and in all subsequent lower age groups.

7.1.1.3 Protocol

Inclusion Criteria:

Subjects must have been in the pediatric age group, from 3 months to 12 years of age, of either sex and of any race, and in general good health (non-immunocompromised, ie, immunocompetent).
A clear diagnosis of atopic dermatitis must have been established
Subjects must have had disease involvement involving 35% or greater body surface area (BSA).
The overall disease must have been moderate to severe and the total sign/symptom score must have been at least 9.
Subjects and their parents/legal guardians must have abided by the restrictions, and returned for all required visits.
Subjects and/or their parents/legal guardians must have signed the statement of informed consent.
Subjects must have had normal or clinically acceptable morning serum cortisol levels and normal HPA responsiveness as determined by a baseline (pretreatment) Cortrosyn stimulation test.

Results of blood chemistry and hematology tests must have been within normal or clinically acceptable limits.

Exclusion Criteria:

Female subjects who were lactating, pregnant, or sexually active
Subjects with a known hypersensitivity to any components of the study drug
Subjects requiring any other medication (topical or systemic) that may have affected the HPA axis, the course of the disease during the study period or affected topical safety (eg, a topical retinoid)
Subjects who had taken immunosuppressive medication (including systemic steroids) within one month prior to Study Day 1
Subjects having chronic diseases (eg, diabetes, renal hepatic) which could have interfered with interpretation of the study results.
Subjects previously enrolled in the study
Subjects who had received any experimental drugs within 30 days prior to Study Day 1
Subjects with clinical signs of pre-existing skin atrophy, telangiectasia or striae in, or nearby, treatment areas
Subjects receiving any other experimental therapy or currently participating in another clinical study
Subjects with suspected cutaneous infection of the skin
Subjects who had used topical corticosteroids within 7 days prior to enrollment or systemic corticosteroids 28 days prior to enrollment

Study Plan: Subjects were to apply the medication to the affected areas of the body bid. Treated areas could include the face (excluding the eye region), scalp, palms and soles of the feet in addition to the body. Treatment of the face or forehead was at the discretion of the investigator. Patients returned to clinic after two weeks of treatment. If clear, exit safety evaluations were performed. If not, patients were treated for 1 more week for a total of 3 weeks before end-of-treatment safety evaluations were performed.

Baseline testing of the integrity of the HPA axis (Visit 1) was to be done prior to initiation of treatment of study day 1. HPA axis testing was to be repeated at the end of treatment (visit 3, day 15, or visit 4, day 22). The procedure consisted of drawing approximately 5 ml of whole blood to carry out the serum cortisol determination. Through the same IV cannula, the appropriate weight-adjusted dose of Cortrosyn® in 2 – 5 ml of normal saline was then to be injected over a 2-minute period. The Cortrosyn® dose for a child weighing ≥ 15 kg was to be 0.25 mg, and for a child weighing < 15 kg was to be 0.125 mg. Thirty minutes later, another 5 ml of blood was obtained to determine the post-Cortrosyn® serum cortisol determination.

Serum cortisol levels (from the central laboratory) for these age groups were used as the reference range. For these studies, a normal response to the Cortrosyn® test at 30 minutes was defined as at least a 7 μg/100 ml incremental rise from the pre-challenge serum cortisol level or a post-Cortrosyn® challenge serum cortisol level of at least 18 μg/100 ml.

Only subjects with normal or clinically acceptable baseline values for blood chemistry, hematology and serum cortisol, and with a normal response to the Cortrosyn® test before treatment, were to be included in the study. Subjects could be empanelled in the study and begin using study medication pending the results of the tests. If the response to Cortrosyn® stimulation was abnormal or clinically unacceptable, the Investigator was to drop the subject from the study

and enroll another in his or her place. Subjects who had an abnormal morning serum cortisol level or an abnormal cortisol response at end of treatment (visit 3, day 15; or visit 4, day 22) were to have these tests repeated at the time of the first follow-up visit and, if continued abnormal, were to be followed as medically necessary.

Subjects were to be followed for adverse events, specifically also looking at the skin and appendageal system for adverse events known to be possible with use of a topical corticosteroid.

Reviewer's Comment: *A meeting concerning this submission was held between the sponsor and the Agency (including the office director of ODE V) on March 19, 2001 at which the criteria for an abnormal response to the Cortrosyn® stimulation test was discussed. A point of clarification was made concerning the pediatric written request and the Cortrosyn® stimulation test. The Agency advised that the determination of adrenal suppression should follow the Cortrosyn® labeling because this is the test that is being used. Specifically, in the label, the following was noted,* "Many patients with normal adrenal function, however, do not respond to the expected degree so that the following criteria have been established to denote a normal response:

1. The control plasma cortisol level should exceed 5 micrograms/100mL.
2. The 30-minute level should show an increment of at least 7 micrograms/100mL above the basal level.
3. The 30-minute level should exceed 18 micrograms/100 mL."

The company agreed to reanalyze the data according to the criteria delineated in the label and resubmit it. The reanalysis was submitted June 1, 2001.

7.1.1.3.1 Population

Subjects who were 3 months – 12 years old with moderate to severe atopic dermatitis that involved at least 35% total body surface area.

7.1.1.3.2 Endpoints

Safety Endpoints

Assessment of HPA axis function via Cortrosyn testing. This was to be evaluated at visit 1 (baseline)prior to treatment on day 1, and end of treatment, visit 3 (day 15) or 4 (day 22). Subjects who had an abnormal morning serum cortisol level or an abnormal cortisol response at end of treatment (visit 3, day 15; or visit 4, day 22) were to have these tests repeated at the time of the first follow-up visit and, if continued abnormal, were to be followed as medically necessary.

Cutaneous assessment of the following clinical signs: telangiectasia, shininess, thinness, striae, bruising, loss of elasticity, and loss of normal skin markings. Signs of cutaneous atrophy would be assessed with 2x magnification but would also be labeled "overt", if observations of the signs could be made with the unaided eye. A subgroup analysis of the face was to be performed. This assessment occurred at all 6 visits.

Subjects also had routine laboratory tests performed that consisted of chemistry, hematology, and urinalysis. A clinically meaningful laboratory value was any shift in value from

baseline to >3 times the upper or <1/3 the lower limit of normal at endpoint. This assessment occurred at baseline (visit 1) and end of treatment (visit 3 or 4).

"Rate-limiting safety" factors were defined as the occurrence of at least one of the following:

- Deviation (reduction) of 10% (or greater) from the lower normal limit for serum cortisol and/or an abnormal Cortrosyn® (cosyntropin) challenge response in 10% of subjects within any one of the age groups.
- Presence of overt atrophy in 5% (or greater) of subjects in any one age group.
- Development of treatment-emergent adverse events of moderate or greater severity in 10% (or greater) of subjects in any one age group.
- Presence of any of the individual signs of atrophy of moderate or greater severity in 5% (or greater) of subjects in any one age group.
- Presence of striae of any degree in any subject in any one age group.

Reviewer's Comment: *The rate-limiting safety factors were requested by the sponsor and after a teleconference with the sponsor, the Agency issued an amended written request including these rate-limiting safety factors.*

7.1.1.4 Results

7.1.1.4.1 Populations enrolled/analyzed

There were a total of 63 subjects with moderate to severe disease enrolled at six sites in this study and treated with study medication. There were two additional sites that did not enroll any subjects. The age range across all age groups in this study was 1.16 years to 11.47 years. Sixty-seven percent of subjects were male, 33% were female; 49% were Caucasian, and 46% were Black. The mean percent of BSA disease involvement was 46% (range: 35% to 90%). Ten percent of subjects had treatment areas that included the face, 90% had treatment areas that were only on the trunk and extremities. See table 1 for full baseline demographics.

Table 1
Baseline Demographics
ITT Population

Demographic Characteristic	Age Group				Total (n=63)
	3 mo – 1 yr (n=7)	2 yr – 5 yr (n=27)	6 yr – 8 yr (n=20)	9 yr – 12 yr (n=9)	
Age (yr)					
Mean (SD)	1.59 (0.32)	4.06 (1.36)	7.47 (0.78)	10.52 (0.77)	5.79 (2.91)
Median	1.68	4.12	7.43	10.88	5.73
Range	1.16 - 1.94	2.11 - 5.99	6.10 - 8.85	9.56 - 11.47	1.16 - 11.47
Gender (n [%])					
Female	2 (29)	10 (37)	8 (40)	1 (11)	21 (33)
Male	5 (71)	17 (63)	12 (60)	8 (89)	42 (67)
Race (n [%])					
Caucasian	2 (29)	13 (48)	11 (55)	5 (56)	31 (49)
Black	5 (71)	11 (41)	9 (45)	4 (44)	29 (46)
Other	0 (0)	3 (11)	0 (0)	0 (0)	3 (5)
Height/Length (in)					
Mean (SD)	30.9 (3.6)	37.9 (7.7)	49.8 (4.5)	59.9 (3.8)	44.0 (10.8)
Median	31.0	39.0	49.5	60.2	45.0
Range	24 - 36	21 - 48	40 - 60	54 - 65	21 - 65
Weight (lb)					
Mean (SD)	24.9 (2.4)	40.6 (10.3)	62.1 (19.7)	113.0 (33.2)	56.0 (31.6)
Median	25.0	38.0	56.7	118.2	48.5
Range	22 - 28	27 - 60	40 - 125	70 - 165	22 - 165
Body Surface Area Involvement (%)					
Mean (SD)	43.3 (12.3)	49.6 (17.6)	44.6 (14.9)	40.1 (3.4)	45.9 (15.0)
Median	40.0	45.0	40.0	40.0	40.0
Range					
Overall Disease Status[a]					
Mean (SD)	2.6 (0.5)	2.4 (0.5)	2.5 (0.5)	2.4 (0.5)	2.5 (0.5)
Median	3.0	2.0	2.0	2.0	2.0
Clinical Signs/Symptoms Total Severity Index[b]					
Mean (SD)	12.9 (1.9)	12.4 (2.4)	12.0 (2.2)	11.4 (1.7)	12.2 (2.2)
Median	13.0	13.0	12.0	12.0	12.0
Range					
Treatment Area (n [%])					
Face[c]	0 (0)	5 (19)	1 (5)	0 (0)	6 (10)
Trunk and Extremities Only	7 (100)	22 (81)	19 (95)	9 (100)	57 (90)

a: Overall disease status: 1 = mild, 2 = moderate, 3 = severe.

b: Total severity index is the total of the individual scores (0 = none, 1 = mild, 2 = moderate, 3 = marked or severe) for the disease signs/symptoms (erythema, induration/lichenification, exudation, skin surface disruption, excoriation, pruritus).

c: In addition to trunk and extremities.

Source Data: **Sections 14.1.3., 14.2.1., 14.2.2., 14.3.6.3., 14.3.6.4., 16.2.6.3., 16.2.13.1., and 16.2.13.2.**

Of these 63 subjects, 47 (75%) completed the full 3-week treatment regimen. Nineteen of these 47 subjects (30%) completed the 2-week follow-up visit only, and 28 (44%) completed both the 2-week and 4-week follow-up visits. Sixteen subjects (25%) discontinued treatment prior to completing the entire treatment regimen: one subject due to disease clearing and 15 subjects due to other reasons. Of these 15 subjects who discontinued treatment due to other reasons, eight were due to early closure of the study. Five subjects who discontinued treatment did not complete any follow-up visit.

Overall, 89% (56/63) of subjects completed at least 14 days of treatment, while 75% (47/63) of subjects completed at least 21 days of treatment. The mean number of treatment days for all subjects was 19.7 with a range of 2 to 37 days. Across the four age groups, mean therapy durations ranged from 15.7 days (3-month to 1-year age group) to 21. Days (9- 12-year age group). The mean cumulative study drug use for all subjects was 46.5 grams. The minimum known total amount of study drug applied by any one subject was 2.1 grams (subject 05/19), while the maximum known total amount applied was 125.1 grams (subject 07/06).

Reviewer's Comment: *All of the patients in the ITT population (63/63) are evaluable for local tolerance of Diprosone Cream, 0.05%. However, for the evaluation of the hypothalamic-pituitary-adrenal axis, 11 patients will be excluded from the evaluation, as a major protocol violation occurred. According to Cortrosyn® labeling, these patients did not meet the criteria for a normal response at baseline during the stimulation testing and therefore should have been excluded from the study. Table 2 shows their results at baseline.*

Table 2
Patients with Baseline Adrenal Suppression

Center/Subject	Sex/Age/Race[a]	Serum Cortisol Concentration (µg/dL)*		
		Baseline		
		Pre	Post	Stim Change
0005/000009	M/6yr 10mo/C	22.87[b]	27.47[c]	**4.60**[d]
0005/000019	M/6yr 1mo/C	15.30	19.90	**4.60**
0006/000003	M/9yr 6mo/N	8.26	**16.67**	8.41
0006/00004	M/8yr 16dy/C	19.50	25.08	**5.58**
0006/000009	F/8yr 3mo/C	6.67	**16.49**	9.82
0006/000010	F/11yr 2mo/N	**3.59**	**17.69**	14.10
0006/000019	F/5yr 7mo/N	3.37	13.59	10.22
0006/000025	F/1 yr 11mo/N	-	**7.18**	-
0006/000028	M/7yr 7mo/C	8.26	**17.87**	9.61
0006/000030	M/4yr 11m0/N	**2.68**	25.19	22.51
0007/000003	M/5yr 11mo/N	10.58	**17.87**	7.29

[a]C=Caucasian
N=non-Caucasian
*bolded values indicate abnormality

b=should exceed 5 µg/dL
c=should exceed 18 µg/dL
d=the change between pre and post should be at least 7 µg/dL

Reviewer's Comment: *Another seven subjects (05/15, 05/18, 05/20, 06/16, 06/22, 07/05, and 08/01) are excluded from the final analysis of HPA axis suppression as there was not any endpoint (end-of-treatment) values for cortisol recorded. Subject 05/03 is being excluded because the subject used a prohibited medication, fluticasone propionate spray during the trial.*

Subject 07/02 is being excluded because the subject erroneously received the higher dose of cortrosyn at baseline which makes subsequent results unreliable. Table 3 lists these patients and their demographics.

Table 3
Additional Subject Exclusions

Center/Subject	Sex/Age/Race*
0005/000015	M/2yr 5mo/N
0005/000018	M/1yr 9mo/N
0005/000020	M/1yr 10mo/N
0006/000016	F/ 6yr 8mo/N
0006/000020	M/2yr 8mo/N
0006/000022	M/5yr 28dy/N
0007/000005	M/ 2yr 1mo/N
0008/000001	M/1yr 7mo/C
0005/000003	M/8yr 8mo/N
0007/000002	F/3yr 8mo/C

*C=Caucasian N=nonCaucasian

Finally, subject 05/04 will remain in the population to be evaluated although the patient erroneously received Lotrisone Cream to use instead of Diprosone Cream, as the chemical entity being evaluated, betamethasone dipropionate, is in both drug products at the same concentration.

7.1.1.4.2 Safety outcomes

There are 43 patients (43/63), 68% of the ITT population that are evaluable for HPA axis suppression. Eleven patients are excluded because they exhibited suppression upon entry into the study, seven because at the end of treatment, some part of the Cortrosyn stimulation test was not obtained and two others because of the circumstances described above under the reviewer's comment. The total number of evaluable patients per age group for HPA axis suppression and for cutaneous side effects known to occur with topical corticosteroids (e.g. atrophy) is delineated in table 4.

Table 4
Evaluable Patients by Age Group

Age Group	3 mo – 1 yr	2 yr – 5 yr	6 yr – 8 yr	9 yr – 12 yr
HPA axis evaluation (N=43)	3	20	13	7
Cutaneous evaluation (N=63)	7	27	20	9

HPA Axis Evaluation Results

A total of 10 of the 43 evaluable patients (23%) had abnormal pre-Cortrosyn® stimulation serum cortisol values, abnormal post-Cortrosyn® stimulation serum cortisol values, and/or abnormal pre/post-Cortrosyn® stimulation change in serum cortisol values at endpoint (either 2 or 3 weeks of treatment). Table 5 is a listing of these 10 subjects with their baseline and endpoint serum cortisol levels. A 2-week follow-up is shown for those patients who had a repeat test.

Table 5
Subjects with Evidence of Adrenal Suppression At Endpoint[1]
Evaluable Patients (N=43)

Subject	Sex/Age	Serum Cortisol Concentration (µg/dL)#								
		Baseline			Endpoint			2-week Follow-up		
		Pre	Post	Stim Change	Pre	Post	Stim Change	Pre	Post	Stim Change
05/05	M/7yr 2mo	12.40	21.89	9.49	12.47	18.77	**6.30[a]**	*	*	*
05/06	M/6yr 9mo	9.17	21.09	11.92	9.39	**15.69[b]**	**6.30**	*	*	*
05/10	M/4yr 1mo	9.89	22.98	13.09	**2.46[c]**	**8.88**	**6.42**	*	*	*
05/13	M/5yr 2mo	10.58	26.39	15.81	16.49	18.19	**1.70**	*	*	*
06/02	M/11yr 1dy	5.69	20.37	14.68	6.20	**16.27**	10.07	*	*	*
06/27	M/5yr 8mo	7.29	20.77	13.48	**2.68**	19.68	17.00	*	*	*
07/01	F/2yr 9mo	8.08	23.89	15.81	**3.77**	18.59	14.82	**24.86**	**12.18**	**-12.68**
07/04	M/7yr 2mo	12.98	24.39	11.41	12.29	18.09	**5.80**	14.68	21.78	7.10
07/06	M/2yr 6mo	9.79	23.49	13.70	**0.98**	**3.99**	**3.01**	*	*	*
07/07	M/2yr 6mo	10.69	22.98	12.29	7.68	**11.60**	**3.92**	*	*	*

[1]Adapted from table 1.1, attachment 1, volume 14.1, pgs. 215-216
#abnormal values are bolded a- should be at least 7ug/dL; b- should be >18 ug/dL; c- should be > 5ug/dL
* not done

Reviewer's Comment: *No subject listed under protocol deviations in this group received an inappropriate dose for weight of Cortrosyn®.*

Table 6 shows the number of subjects with HPA axis suppression by age group.

Table 6
HPA Axis Suppression by Age Group
Evaluable Subjects

Age Group	3mo-1yr n=3	2yr-5yr n=20	6yr-8yr n=13	9yr-12yr n=7
No. suppressed	0	6	3	1
%	0	30	23	14

Reviewer's Comment: *Tables 5 and 6 reveal that there is a significant amount of adrenal suppression with use of Diprosone Cream, 0.05% in the pediatric population. This occurs with patients using the drug as labeled. As shown in table 6, the range of adrenal suppression is from 14% in the 9-12 year old group up to 30% in the 2-5 year old group. The study was aborted because the sponsor found rate-limiting safety of 10% suppression. Subjects 3 months – 1 year of age should not have been enrolled. Most likely, seeing the trend, if more patients had been studied in this age group, HPA suppression would have been found, also. Two of the 10 patients who demonstrated adrenal suppression (20%) had a follow-up Cortrosyn® stimulation test. One subject showed recovery of the hypothalamic pituitary adrenal axis. Unfortunately, there are no 2-week follow-up results for the remaining 8 patients (80%) who exhibited evidence of suppression.*

In this reviewer's opinion, given that atopic dermatitis is the most common corticosteroid responsive disease in children for which a drug product such as this would be used, and given that atopic dermatitis is a remitting and relapsing disease, and even assuming recovery of the adrenal gland on cessation of the medication, and given the probability of repeated insult to the adrenal gland with Diprosone Cream, 0.05% during the developing months of infancy and childhood, it would be unwise to use this medication in children 12 years of age or younger.

Statistical review by Dr. Shiowjen Lee did not reveal a statistically significant effect of number of days treated, age, or weight in the development of HPA axis suppression. There was a statistical significance in the mean amount of drug used, 81 grams vs 37 grams for subjects suppressed vs not suppressed ($p<0.001$). There was a numerically higher %BSA involvement in subjects who were suppressed and also numerically more males developed suppression (see statistical consult for full details).

Cutaneous Safety

Reviewer's Comment: *According to the sponsor,* "Adverse reactions reported to be possibly or probably related to treatment with DIPROSONE Cream during a pediatric clinical study include: nasal congestion and a fungal infection. These reactions occurred in 2 different patients out of 55 patients, 1% respectively.[5]" *This is the sponsor's current assessment of the data that was submitted as a reanalysis of the data.*

However, in the first submission, the label assessed the cutaneous safety as follows, "In an uncontrolled study, fungal infections were observed in 2% of 63 pediatric subjects ages 1 to 12 years. A sign of skin atrophy (bruising) was observed in 5% of 63 subjects (ages 1 to 12 years) during treatment or one day following cessation of treatment."

The following text is an assessment of my review of the raw data (line listings) for each patient, which is consistent with the sponsor's first assessment.

The ITT population (N=63) was evaluable for cutaneous safety (refer to table 4). Clear-cut treatment emergent cutaneous atrophy, whether viewed with 2x magnification or with the naked eye occurred in 3 of the 63 patients (5%) treated with Diprosone Cream, 0.05%. These three cases occurred in the truncal and/or extremity areas. Patient 01/02, a 3 year old, had mild bruising on day 22; patient 01/03, a 5 year old, had mild shininess noted on day 24; and patient 05/05, a 7 year old, had moderate bruising on day 8. All three patients had resolution of the

potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are prescribed for a nursing woman.

Pediatric Use DIPROSONE Ointment is not recommended in pediatric patients 12 years of age and younger. (See **CLINICAL PHARMACOLOGY** and **ADVERSE REACTIONS** Sections.)

In an open label study, 15 of 53 (28%) evaluable pediatric patients (aged 6 months – 12 years old) using DIPROSONE Ointment for treatment of atopic dermatitis demonstrated HPA axis suppression. The proportion of patients with adrenal suppression in this study was progressively greater, the younger the age group. (See **CLINICAL PHARMACOLOGY - Pharmacokinetics.**) Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio. The study described above supports this premise as adrenal suppression in 9-12 year olds, 6-8 year olds, 2-5 year olds, and 3 months – 1 year old was 17%, 27%, 29%, and 36%, respectively.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients.

atrophy on follow-up. Six subjects received treatment to the face. There were no reports of atrophy to this area.

Laboratory Safety

There was 1 subject that exhibited clinically meaningful laboratory results after the start of treatment. Subject 06/18 exhibited an elevated ALT value of 101 (normal range = 5 to 30 U/L) on day 23, one day following the last application of study medication. Baseline ALT for this subject was normal. In addition to the elevated ALT value, this subject also exhibited an elevated AST value at endpoint of 105 U/L (normal range 0 to 69 U/L) that was normal at baseline. Repeat of these laboratory parameters were not obtained at follow-up.

Reviewer's Comment: *Topical steroids are not known to alter LFTs. Without follow-up results and workup of this patient, it is not possible to ascertain whether this result is secondary to Diprosone Cream, 0.05%.*

8 Safety Conclusions

This study clearly demonstrates that Diprosone Cream, 0.05% has a poor safety profile in pediatric patients. The primary systemic safety factor, HPA axis suppression, occurred in a significant proportion of pediatric patient ages 2 – 12 years old after treatment with Diprosone Cream, 0.05% under labeled conditions for atopic dermatitis. This range of suppression is from 14% in 9-12 year olds, to 30% in 2-5 year olds. The secondary safety variable of cutaneous atrophy revealed a 5% overall incidence of cutaneous atrophy.

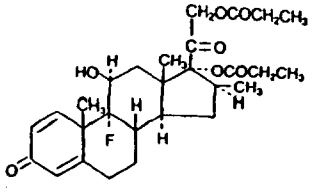
9 Labeling Review

Reviewer's Comment: *The following is the final draft label submitted by the sponsor dated 5/01. Deletions are noted by ~~strikeout~~ and additions by shadowing.*

9.1 Description

DESCRIPTION DIPROSONE Cream contains betamethasone dipropionate, USP, a synthetic adrenocorticosteroid, for dermatologic use. Betamethasone, an analog of prednisolone, has high corticosteroid activity and slight mineralocorticoid activity. Betamethasone dipropionate is the 17, 21-dipropionate ester of betamethasone.

Chemically, betamethasone dipropionate is 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula $C_{28}H_{37}FO_7$, a molecular weight of 504.6, and the following structural formula:



Betamethasone dipropionate is a white to creamy white, odorless crystalline powder, insoluble in water.

Each gram of DIPROSONE Cream 0.05% contains: 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone) in a hydrophilic emollient cream consisting of purified water, USP; mineral oil, USP; white petrolatum, USP; ceteareth-30; cetearyl alcohol 70/30 (7.2%); sodium phosphate monobasic monohydrate R; and phosphoric acid, NF; chlorocresol and propylene glycol, USP as preservatives. May also contain sodium hydroxide R to adjust pH to approximately 5.0.

9.2 Clinical Pharmacology

CLINICAL PHARMACOLOGY The corticosteroids are a class of compounds comprising steroid hormones, secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses corticosteroids are used primarily for their anti-inflammatory and/or immunosuppressive effects.

Topical corticosteroids, such as betamethasone dipropionate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, antipruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of their actions in each disease are uncertain. Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

Pharmacokinetics The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. (See **DOSAGE AND ADMINISTRATION**.)

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See **DOSAGE AND ADMINISTRATION**.)

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

Sixty-three pediatric patients ages 1 to 12 years, with atopic dermatitis, were enrolled in an open-label, hypothalamic-pituitary-adrenal (HPA) axis safety study. DIPROSONE Cream

was applied twice daily for 2 to 3 weeks over a mean body surface area of 40% (range 35% to 90%).

In 10 of 43 (23%) patients, adrenal suppression was indicated by either a ≤ 5 mcg/dL pre-stimulation cortisol, or a cosyntropin post-stimulation cortisol ≤ 18 mcg/dL and/or an increase of <7 mcg/dL from the baseline cortisol.

Studies performed with DIPROSONE Cream indicate that it is in the medium range of potency as compared with other topical corticosteroids.[3]

9.2 Indications and Usage

DIPROSONE Cream is a medium-potency corticosteroid[3] indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

9.4 Contraindications

DIPROLENE AF Cream is contraindicated in patients who are hypersensitive to betamethasone dipropionate, to other corticosteroids, or to any ingredient in this preparation.

9.5 Precautions

9.5.1 General

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. (See **DOSAGE AND ADMINISTRATION**.)

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary-free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. In an open-label pediatric study, of the 10 subjects who showed evidence of suppression, 2 subjects were tested 2 weeks after discontinuation of Diprosone Cream, 0.05%; and 1 of the 2 (50%) had complete recovery of HPA axis function. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Pediatric patients may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See **PRECAUTIONS -Pediatric Use.)**

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

9.5.2 Information for patients

This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive. (See **DOSAGE AND ADMINISTRATION.)**
4. Patients should report any signs of local adverse reactions.

9.5.3 Laboratory tests

The following tests may be helpful in evaluating HPA axis suppression:

Urinary-free cortisol test
ACTH stimulation test

9.5.4 Carcinogenesis, mutagenesis, impairment of fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential

9.5.5 Pregnancy

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

[redacted]

9.5.6 Nursing mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are prescribed for a nursing woman.

9.5.7 Pediatric use

[redacted] Use of Diprosone Cream, 0.05% in pediatric patients 12 years of age and younger is not recommended.

[redacted]

(See **CLINICAL PHARMACOLOGY - Pharmacokinetics.**)

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio. The study described above supports this premise, as suppression in 9-12 year olds, 6-8 year olds, and 2-5 year olds was 14%, 23%, and 30%, respectively.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients.

9.6 Adverse Reactions

The following local adverse reactions are reported infrequently when DIPROSONE Cream is used as recommended in the **DOSAGE AND ADMINISTRATION** section. These reactions

are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, miliaria.

Adverse reactions reported to be possibly or probably related to treatment with Diprosone Cream during a pediatric clinical study include signs of skin atrophy (bruising, shininess). Skin atrophy occurred in 3 of 63 (5%) patients, a 3-year-old, a 5-year-old and a 7-year- old.

9.9 Overdosage

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See **PRECAUTIONS.**)

9.10 Dosage and Administration

Apply a thin film of DIPROSONE Cream 0.05% to the affected skin areas once daily. In some cases, a twice-daily dosage may be necessary.

DIPROSONE Cream is not to be used with occlusive dressings.

9.11 How Supplied

DIPROSONE Cream 0.05% is supplied in 15-g (NDC 0085-0853-02) and 45-g (NDC 0085-0853-03) tubes; boxes of one.

Store DIPROSONE Cream between 2° and 30°C (36° and 86°F).

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. D 5/01

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YYYYYYYYYT

10 Recommendation

It is recommended that Diprosone Cream, 0.05% not be approved for use in pediatric patients 12 years of age and younger. The label should be changed to reflect the additional safety information demonstrated in this age group that supports this restriction.

Denise Cook, M.D.
Medical Officer, Dermatology

cc: HFD-540
HFD-340
HFD-540/CSO/CintronO
HFD-540/MO/CookD
HFD-880/Biopharm/Bashaw
HFD-725/Stats/Leesh
Draft 7/14/01
In DFS 7/18/01

For Concurrence Only:
HFD-540/Clinical TL/WalkerS
HFD-540/DivDir/WilkinJ