CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-691/S-019

17-691/S-024

MEDICAL REVIEW

Medical Officer's Review of NDA 17-691

Efficacy Supplement

NDA #17-691
Serial#: SE5-024
HFD#1: 006674

HFD#2: 018165

Submission date: 10/04/00
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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 Ointment, 0.05%
Pharmacologic Category:	Anti-inflammatory
Indication(s):	Corticosteroid responsive dermatoses
Dosage Form(s):	Ointment
Route (s) of Administration:	Topical
Related Drugs:	Diprosone Cream – NDA 17-536 Diprosone Lotion – NDA 17-781 Diprolene AF Cream – NDA 19-555
Related Review:	Statistics draft 7/07/01

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3 Regulatory Background

This supplement is being submitted to determine the safety of use of Diprosone Ointment, 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 submitted by the sponsor (October 5, 2000 for the label are shadowed in gray. The 2nd proposed changes that were submitted with the reanalysis of the data on June 1, 2001 are underlined.)

5.1 Proposed Clinical Pharmacology

Eighty pediatric patients ages 6 months to 12 years, with atopic dermatitis, were enrolled in an open-label hypothalamic-pituitary-adrenal (HPA) axis safety study. DIPROSONE Ointment was applied twice daily for 2 to 3 weeks over a mean body surface area of 58% (range 35% to 99%).

patients, adrenal suppression was indicated by either a pre-stimulated cortisol concentration 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. patients demonstrated a normally responsive HPA axis.

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

5.2 Proposed Indications and Usage

INDICATIONS AND USAGE DIPROSONE Ointment is a high-potency corticosteroid[3] indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive-dermatoses in patients

5.3 Proposed Pediatric Use

Pediatric Use Use of DIPROSONE OINTMENT

Pediatric Use

5.4 Proposed Adverse Reactions

Adverse reactions reported to be possibly or probably related to treatment with DIPROSONE Ointment during a pediatric clinical study include

5.5 Proposed Dosage and Administration

6 Description of Clinical Sources

Study PO1261 – This is an open-label, multicenter, safety study of Diprosone Ointment, 0.05% conducted in response to a pediatric written request. The study was to evaluate the systemic and cutaneous safety of Diprosone Ointment, 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 21, 2000 to October 20, 2000 in which 80 subjects were enrolled. 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 # - PO12061

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

7.1.1 Investigators

1.	Alice Gottlieb, M.D.	01/New Brunswick, NJ
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7.	Frank E. Schiavone, M.D.	08/Jacksonville, FL
8.	Melinda T.B. Musick, M.D.	09/Huntsville, AL

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 Ointment, 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 form 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

Two populations were analyzed in this study, the intent-to-treat (ITT) population and the modified intent-to-treat (MITT) population. The ITT population was all subjects who were enrolled and who received at least one application of study medication. The MITT population was subjects who received treatment for at least 2 weeks, who had both baseline and end-of-treatment cortisol level evaluations (with Cortrosyn stimulation testing), who had a 2-week post-treatment follow-up, and who met entry criteria. Eighty subjects with moderate to severe disease were enrolled at 6 study sites. Two additional sites did not enroll any subjects. The age range (all age groups) for this study was 0.58 years to 12.62 years. There were 50% female subjects and 50% male subjects, 49% Caucasian subjects and 46% Black subjects. The mean percent of BSA disease involvement for all subjects in this study was 58% (range: 35% to 99%). Treated areas included the face for 29% of the subjects, and areas on trunk and extremities only for 71% of the subjects. See table 1 for full baseline demographics.

Table 1
Summary of Baseline Demographics
ITT Population

Demographic Characteristic	Age Group 3 mo – 1 yr (n=14)	2 yr – 5 yr (n=28)	6 yr – 8 yr (n=27)	9 yr – 12 yr (n=11)	Total (n=80)
Age (yr)					
Mean (SD)	1.46 (0.32)	3.88 (1.28)	7.24 (0.62)	10.84 (0.96)	5.55 (3.10)
Median	1.47	3.86	7.26	10.77	5.94
Range	0.58 - 1.88	2.19 - 5.97	6.03 - 8.15	9.36 - 12.62	0.58 - 12.62
Gender (n [%])					
Female	6 (43)	14 (50)	15 (56)	5 (45)	40 (50)
Male	8 (57)	14 (50)	12 (44)	6 (55)	40 (50)
Race (n [%])					
Caucasian	11 (79)	12 (43)	8 (30)	8 (73)	39 (49)
Black	3 (21)	16 (57)	16 (59)	2 (18)	37 (46)
Other	0 (0)	0 (0)	3 (11)	1 (9)	4 (5)
Height/Length (in)					
Mean (SD)	31.3 (3.2)	39.7 (3.6)	48.9 (2.4)	57.8 (4.1)	44.4 (8.8)
Median	31.0	40.0	48.7	59.0	45.5
Range	26 - 38	34 - 46	45 - 54	51 - 66	26 - 66
Weight (lb)					
Mean (SD)	24.4 (3.9)	38.8 (9.9)	62.1 (16.5)	101.7 (33.8)	52.8 (29.1)
Median	24.5	37.0	61.0	110.0	45.5
Range	17 - 31	27 - 67	45 - 106	61 - 169	17 - 169
Body Surface Area Involvement (%)					
Mean (SD)	66.9 (19.9)	63.9 (23.5)	52.6 (17.5)	46.1 (17.9)	58.2 (21.2)
Median	62.0	62.0	45.0	40.0	52.0
Range	[redacted]				
Overall Disease Status[a]					
Mean (SD)	2.5 (0.5)	2.4 (0.5)	2.3 (0.4)	2.3 (0.5)	2.4 (0.5)
Median	2.5	2.0	2.0	2.0	2.0
Clinical Signs/Symptoms Total Severity Index[b]					
Mean (SD)	13.2 (2.3)	12.2 (2.6)	10.8 (1.5)	11.3 (2.3)	11.8 (2.3)
Median	12.5	12.0	11.0	10.0	11.0
Range	[redacted]				
Treatment Area (n [%])					
Face[c]	6 (43)	9 (32)	6 (22)	2 (18)	23 (29)
Trunk and Extremities Only	8 (57)	19 (68)	21 (78)	9 (82)	57 (71)

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.**

Reviewer's Comment: *The study enrolled 80 patients. The sponsor withdrew 2 patients, subject 08/06, a 6-year-old, and 08/16, a 5-year-old, because they did not meet protocol eligibility. They were withdrawn on days 8 and 4, respectively. The ineligible criterion was HPA axis suppression at baseline. Therefore, the ITT population should total 78 patients. The number of patients in the 2 year to 5 year group will be reduced by one to 27 and also in the 6 year to 8 year old group to 26 for all further analyses.*

Seventy-four (95%) of these 78 subjects completed the 3-week treatment phase. Of these 74, two subjects (3%) completed no follow-up visits, 35 subjects (45%) completed only the 2-week follow-up visit, one subject (1%) completed only the 4-week follow-up visit, and 36 subjects (46%) completed both the 2-week and 4-week follow-up visits. There were four subjects (5%) who discontinued treatment prior to completing the 3-week treatment regimen: two subjects because of disease clearing and two because of other reasons (one of these four subjects did not complete any follow-up visit).

Reviewer's Comment: *Of the four patients who discontinued, 3 are evaluable for HPA axis suppression as they did have endpoint testing performed. One subject, 03/05, a 1-year-old, did not have endpoint testing done.*

Overall, 97% (76/78) of subjects completed at least 14 days of treatment, while 82% (64/78) of subjects completed at least 21 days of treatment. The mean number of treatment days for all subjects was 21.71 with a range of 9 to 31 days. Mean therapy durations across the four age groups were similar and ranged from 20.7 days (2-5 year age group) to 22.5 days (both the 3-month to 1-year age group and the 9- to 12-year age group). The mean cumulative study drug use for all subjects was 48.14 grams. The minimum total amount of study drug applied by any one subject was 3.3 g (05/20, 05/21), while the maximum total amount applied was 294.4 g (01/01).

Reviewer's Comment: *All of the patients in the ITT population (78/78) are evaluable for local tolerance of Diprosone Ointment, 0.05%, as a minimum of 9 days of treatment with the drug product was completed. However, for the evaluation of the hypothalamic-pituitary-adrenal axis, 21 patients will be excluded from the evaluation, as a major protocol violation occurred. According to Cortrosyn® labeling, these 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 also includes four patients (03/05, 05/14, 08/13, 08/14) that were excluded because of no endpoint evaluation (last four entries of the table).*

Table 2 – Patients Excluded
Patients with Baseline Adrenal Suppression
Patients with no Endpoint Evaluation[@]

Center/Subject	Sex/Age/Race[a]	Serum Cortisol Concentration (µg/dL)[*]		
		Baseline		
		Pre	Post	Stim Change
0003/000003	F/1yr 5mo/C	20.19[b]	22.98[c]	**2.79**[d]
0003/000007	M/3yr 6mo/C	14.28	20.30	**6.02**
0004/000001	F/10yr 2mo/N	**4.68**	23.60	18.92
0004/000008	F/4yr 2mo/N	13.37	19.50	**6.13**
0004/000009	M/4yr 6mo/N	9.50	**17.40**	7.90
0005/000003	M/9yr 4mo/C	25.59	30.26	**4.67**
0005/000006	F/9yr 10mo/C	**3.70**	24.28	20.58
0005/000018	M/4yr 4mo/N	16.67	20.59	**3.92**
0005/000031	F/7yr 5mo/N	22.40	**12.18**	**-10.22**
0008/000002	M/10yr 3mo/C	8.99	**17.40**	8.41
0008/000003	F/10yr 5mo/N	5.47	**15.30**	9.83
0008/000005	F/6yr 3mo/N	**3.48**	22.18	18.70
0008/000007	F/2yr 5mo/N	5.69	**17.07**	11.38
0008/000008	F/7yr 5mo/N	**4.10**	**14.28**	10.18
0008/000009	M/7yr 11mo/N	**4.49**	18.99	14.50
0008/000010	M/6yr 12dy/N	5.69	**14.10**	8.41
0008/000011	F/7yr 1mo/C	**4.97**	18.38	13.41
0008/000012	F/6yr 9mo/N	15.30	19.28	**3.98**
0008/000017	F/7yr 1mo/N	13.08	18.48	**5.40**
0008/000018	F/7yr 6mo/C	7.29	**14.28**	**6.99**
0008/000019	F/8yr 1mo/N	13.08	**16.56**	**3.48**
No Endpoint Evaluation				
0003/000005	F/1yr 5mo/C	10.98	25.88	14.90
0005/000014	F/6yr 11mo/N	10.08	29.39	19.31
0008/000013	F/3yr 7mo/N	6.89	20.99	14.10
0008/000014	M/1yr 7mo/C	7.18	27.69	20.51

[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
@=last four patients in the list

7.1.1.4.3 Safety outcomes

There are 53 patients (53/78), 68% of the ITT population that are evaluable for HPA axis suppression. Twenty-one patients are excluded because they exhibited suppression upon entry into the study and four because at the end of treatment, some part of the Cortrosyn stimulation test was not obtained. 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 3.

Table 3
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=53)	11	21	15	6
Cutaneous evaluation (N=78)	14	27	26	11

HPA Axis Evaluation Results

A total of 15 of the 53 evaluable patients (28%) 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 4 is a listing of these 15 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 4
Subjects with Evidence of Adrenal Suppression At Endpoint[1]
Evaluable Patients (N=53)

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
01/01	M/11yr 2mo	16.56	29.97	13.41	18.88	23.49	**4.61**	*	*	*
03/06	M/1yr 7mo	9.10	24.28	15.18	18.88	21.38	**2.50**	*	*	*
03/08	F/3yr 3mo	10.58	23.38	12.80	19.90	22.29	**2.39**	*	*	*
04/06	M/1yr 4mo	18.27	30.88	12.61	6.60	**15.77**	9.17	*	*	*
05/28	M/2yr 2mo	10.98	21.38	10.40	5.29	**15.08**	9.79	*	*	*
05/29	M/2yr 6mo	12.29	25.59	13.30	20.77	24.07	**3.30**	*	*	*
05/30	F/5yr 11mo	11.27	20.88	9.61	5.29	**12.29**	7.00	*	*	*
07/01	M/8yr 1mo	14.79	26.68	11.89	15.88	20.19	**4.31**	*	*	*
07/02	M/1yr 4mo	22.18	31.28	9.10	**1.67**	**9.79**	8.12	12.47	28.49	16.02
07/04	M/2y 4mo	7.00	29.18	22.18	**2.68**	**14.90**	12.22	8.77	28.49	19.72
07/05	M/0yr 6mo	9.10	23.38	14.28	19.57	25.59	**6.02**	*	*	*
07/08	M/7yr 1mo	13.66	20.99	7.33	12.87	**14.90**	**2.03**	*	*	*
08/01	M/8yr 1mo	16.17	23.89	7.72	7.58	**15.98**	8.40	*	*	*
08/04	M/8yr 17dy	13.19	24.39	11.20	8.19	**11.20**	**3.01**	*	*	*
08/15	M/4yr 9mo	15.48	24.47	8.99	14.17	18.67	**4.50**	*	*	*

[1]Adapted from table 1.1, attachment 1, volume 14.1, pg. 214
#abnormal values are bolded
* not done

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

Table 5 shows the number of subjects with HPA axis suppression by age group.

Table 5
HPA Axis Suppression by Age Group
Evaluable Subjects

Age Group	3mo-1 yr n=11	2yr-5yr n=21	6yr-8yr n=15	9yr-12yr n=6
No. suppressed	4	6	4	1
%	36	29	27	17

Reviewer's Comment: *Tables 4 and 5 reveal that there is a significant amount of adrenal suppression with use of Diprosone Ointment, 0.05% in the pediatric population. This occurs with patients using the drug as labeled. As shown in table 5, the range of adrenal suppression is from 17% in the 9-12 year old group up to 36% in the 3 month-1 year old group. Two of the 15 patients (13%) had a follow-up Cortrosyn® stimulation test. Both patients showed recovery of their hypothalamic pituitary adrenal axis. Unfortunately, there are no 2-week follow-up results for the remaining 13 patients (87%) who exhibited evidence of suppression. It might be surmised that since 2 of 2 (100%) patients who did receive follow-up testing, showed recovery of the adrenal gland, if the remainder had been tested, many of them might also have shown recovery. However, this cannot be claimed with certainly since the data is not available.*

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 Ointment, 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 amount of drug used, %body surface area involved or weight in the development of HPA axis suppression. There was a significantly higher proportion of males than females who were suppressed (p=0.006). However, there was not a statistical difference between the age groups (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 Ointment during a pediatric clinical study include a mild pustule. It occurred in 1 patient, 1%, of the 80 patients involved in the study." *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, the following local adverse events were each observed in 2 % of 74 pediatric subjects (ages 6 months to 12 years): pustules and rash. Signs of skin atrophy (bruising, telangiectasia, shininess, or thinness) were observed in pediatric patients either during treatment (9% of 74 pediatric patients) or immediately following cessation of treatment."

The following text is an assessment of my review of the raw data (line listings) for each patient, which is different from both conclusions of the sponsor.

The ITT population (N=78) was evaluable for cutaneous safety (refer to table 3). Clear-cut treatment emergent cutaneous atrophy, whether viewed with 2x magnification or with the naked eye occurred in 8 of the 78 patients (10%) treated with Diprosone Ointment, 0.05%. Twenty-three patients applied the drug product to some part of the face. Five of these subjects (22%) developed some form of cutaneous atrophy on the face. There was one 1-year-old, two 3-year-olds, one 7-year-old, and one 8-year-old. One of the 3-year-olds had overt atrophy. All but one patient had resolution of the cutaneous atrophy. This was the 8-year-old (07/01) who at the end of the study continued to have mild telangiectasias of the face.

Seven subjects (9%) experienced treatment emergent cutaneous atrophy of the trunk and/or extremities (non-face). There were two 2-year-olds, two 3-year-olds, and one each of age 7, 8, and 12. One patient, a 3-year-old, had overt atrophy. Five of the seven subjects had resolution of the atrophy by study end. The 12-year-old (05/04) had persistent mild telangiectasia and the 7-year-old (07/08) had persistent loss of normal skin markings. The total number of adverse events for cutaneous atrophy is higher than the number of patients with cutaneous atrophy because 4 of the patients had signs of atrophy in both the face and non-facial areas. Table 6 is a summary of the cutaneous effects by age group of Diprosone Ointment, 0.05% when used as labeled for 2 – 3 weeks.

Table 6
Summary of Cutaneous Atrophy
ITT Population

Cutaneous Atrophy	Age Group			
	3 months- 1 year N[1]=14 (%)	2 years-5 years N[1]=27 (%)	6 years – 8 years N[1]=26 (%)	9 years- 12 years N[1]=11 (%)
Facial	1/6 (17)	2/9 (22)	2/6 (33)	0/2 (0)
Non-Facial	0 (0)	4 (15)	2 (8)	1 (9)
Total	1 (7)	6 (22)	4 (15)	1 (9)

[1] This is the denominator unless otherwise noted.

In this reviewer's opinion, Diprosone Ointment, 0.05% has evidenced its capability of causing significant cutaneous atrophy of the face in the pediatric population. It also caused significant atrophy in the toddler years (ages 2-5) in non-facial areas. It may be that this was not evidenced in the infant group because the numbers were too small.

Other cutaneous events included one case of diaper dermatitis, one case of a pustule, one case of urticaria, and one case of impetigo. There was also one case of furunculosis that began during the 2-week follow-up. None of these patients discontinued because of the adverse event.

Laboratory Results

There were not any clinically meaningful laboratory values that occurred in subjects during this trial that could be attributed to Diprosone Ointment, 0.05%.

8 Safety Conclusions

This study clearly demonstrates that Diprosone Ointment, 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 3 months – 12 years old after treatment with Diprosone Ointment, 0.05% under labeled conditions for atopic dermatitis. This range of suppression is from 17% in 9-12 year olds, to 36% in infants 3 months – 1 year old. The secondary safety variable of cutaneous atrophy revealed a significant amount of cutaneous atrophy ranging from a high of 15% in non-facial areas to 33% in facial areas.

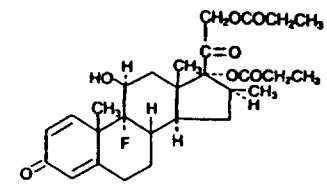
9 Labeling Review

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 Ointment 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 Ointment 0.05% contains: 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone) in an ointment base of mineral oil, USP; and white petrolatum, USP.

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.

Eighty pediatric patients ages 6 months to 12 years, with atopic dermatitis, were enrolled in an open-label hypothalamic-pituitary-adrenal (HPA) axis safety study. DIPROSONE Ointment was applied twice daily for 2 to 3 weeks over a mean body surface area of 58% (range 35% to 99%)

n 15 of 53 evaluable (28%) patients, adrenal suppression was indicated by either a pre-stimulated cortisol concentration ≤ 5 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. Follow-up testing 2 weeks after study completion available for 2 of the patients demonstrated a normally responsive HPA axis.[4]

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

9.3 Indications and Usage

INDICATIONS AND USAGE DIPROSONE Ointment is a high-potency corticosteroid[3] indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive-dermatoses

[redacted]

9.4 Contraindications

CONTRAINDICATIONS DIPROSONE Ointment in patients who are hypersensitive to betamethasone dipropionate, to other corticosteroids, or to any ingredient in these preparations.

9.5 Precautions

9.5.1 General

PRECAUTIONS 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 15 patients who showed adrenal suppression, 2 patients were tested 2 weeks after discontinuation of Diprosone Ointment and both patients showed 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

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

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

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

9.5.5 Pregnancy

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

9.5.6 Nursing mothers

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

Pediatric Use DIPROSONE Ointment

is not recommended in pediatric patients 12 years of age and younger.

[redacted]

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 support this premise as suppression was seen in 9-12 year olds, 6-8 year olds, 2-5 year olds, and 3 months-1 year olds [redacted] 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.

9.6 Adverse Reactions

ADVERSE REACTIONS The following local adverse reactions are reported infrequently when DIPROSONE Ointment 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 Ointment during a pediatric clinical study include [redacted] atrophy (telangiectasia, thinness, shininess, bruising, loss of skin markings) [redacted] Cutaneous atrophy of the face occurred in 1/6 (17%) of infants, 2/9 (22%) of 2-5 year olds, and 2/6 (33%) of 6-8 year olds. Cutaneous atrophy occurred in 15%, 8%, and 9% of 2-5 year olds, 6-8 year olds, and 9-12 year olds respectively.

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.

9.7 Overdosage

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

9.8 Dosage and Administration

[redacted]

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

DIPROSONE Ointment is not to be used with occlusive dressings.

9.9 How Supplied

HOW SUPPLIED DIPROSONE Ointment 0.05% is supplied in 15-g (NDC 0085-0510-04) and 45-g (NDC 0085-0510-06) tubes; boxes of one.

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

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. ~~1/99~~ 5/01

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10 Recommendation

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

Denise Cook, M.D.
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cc: HFD-540
HFD-340
HFD-540/CSO/CintronO
HFD-540/MO/CookD
HFD-880/Biopharm/Bashaw
HFD-725/Stats/Leesh
Draft: 7/09/01
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HFD-540/Clinical TL/WalkerS
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