CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-781/S-015

17-781/S-022

MEDICAL REVIEW

Medical Officer's Review of NDA 17-781

Efficacy Supplement

NDA#:17-781
SE#: SE 5-022/BZ
HFD#1: 006673

HFD#2: 018166

Submission date: 10/04/00
CDER Stamp date: 10/05/00
CDER Stamp date :Reanalysis submitted: 6/01/01
Review initiated: 10/10/00
Review completed: 7/16/01

Sponsor:	Schering Corporation 2000 Galloping Hill Road Kenilworth, New Jersey 07033
Generic name:	Betamethasone dipropionate
Trade name:	Diprosone Lotion, 0.05%
Pharmacologic Category:	Anti-inflammatory
Indication(s):	Corticosteroid responsive dermatoses
Dosage Form(s):	Lotion
Route (s) of Administration:	Topical
Related Drugs:	Diprosone Ointment – NDA 17-691 Diprosone Cream – NDA 17-536 Diprolene AF Cream – NDA 19-555
Review:	Statistics review – draft 7/12/01

2 **Table of Contents**

3 Regulatory Background

This supplement is being submitted to determine the safety of use of Diprosone Lotion, 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 June 1, 2001 with the reanalysis of the data are underlined.)

5.1 Proposed Clinical Pharmacology

[redacted]

Twenty-five pediatric patients ages 6 to 12 years, with atopic dermatitis, were enrolled in an open-label, hypothalamic-pituitary-adrenal (HPA) axis safety study. DIPROSONE Lotion was applied twice daily for 2 to 3 weeks over a mean body surface area of 45% (range 35% to 72%).

[redacted] patients, adrenal suppression was indicated by either a [redacted] 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 Lotion indicate that it is in the medium range of potency as compared with other topical corticosteroids.[3]

5.2 Proposed Indication and Usage Section

[redacted]

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

5.3 Proposed Pediatric Use Section

[redacted]

5.4 Proposed Adverse Reactions Section

[redacted]

Adverse reactions reported to be possibly or probably related to treatment with DIPROSONE Lotion during a pediatric study include: paresthesia (burning), erythematous rash, and dry skin. These adverse reactions each occurred in a different patient; 4% of the 25 patient population, respectively. An adverse reaction reported to be possibly or probably related to treatment in 2 different patients, 8%, of the 25 patients is puritus.[5]

5.5 Proposed Dosage and Administration Section

[redacted]

6 Description of Clinical Data Source

Study PO1263 – This is an open-label, multicenter, safety study of Diprosone Lotion, 0.05% conducted in response to a pediatric written request. The study was to evaluate the systemic and cutaneous safety of Diprosone Lotion, 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 7, 2000 to May 13, 2000 in which 25 subjects were enrolled. This study was aborted before any subjects 5 years and younger could be enrolled because it reached "rate-limiting" safety in the higher age groups. 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 # - PO1263

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

7.1.1 Investigators

1.	Gloria Campbell D'Hue, M.D.	01/Atlanta, GA
2.	Libby Edwards, M.D.	02/Charlotte, NC
3.	Frank E. Schiavone, M.D.	04/Jacksonville, FL
4.	Steven C. Shapiro, M.D.	06/Hattiesburg, MS
5.	Robert J. Kaplan, M.D.	07/Memphis, TN

7.1.1.1 Objective/Rationale

The objective of the study was to determine both the local and systemic safety of Diprosone Lotion, 0.05% in pediatric patients12 years of age down to 3 months of age. The primary safety variable was the assessment of the hypothalamic-pituitary-adrenal (HPA) axis through Cortrosyn® stimulation testing.

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

Twenty-five subjects with moderate to severe disease were enrolled in two of the five sites. Nineteen subjects (76%) were treated for a full 3 weeks and also completed the 2-week follow-up phase; 6 subjects (24%) were discontinued from treatment (five due to early closure of the study). Four subjects (16%) completed 2 weeks of treatment and 2 weeks of follow-up; 23 (92%) were treated for either 2 or 3 weeks and completed the 2-week follow-up phase.

The age range of subjects was 6.50 years to 12.90 years. Seventy-six percent of the subjects were female, 24% were male; 60% were Black, and 40% were Caucasian. The mean percent BSA involvement for all ages groups was 45% (range 35% to 72%). All subjects received treatment on the trunk and extremities only. See table 1 for full baseline demographics.

Table 1
Baseline Demographics
ITT Population

Demographic Characteristic	Age Group				Total
	3 mo – 1 yr (n=0)	2 yr – 5 yr (n=0)	6 yr – 8 yr (n=17)	9 yr – 12 yr (n=8)	(n=25)
Age (yr)					
Mean (SD)			7.63 (0.76)	10.61 (1.29)	8.58 (1.70)
Median			7.66	10.65	7.95
Range			6.50 - 8.97	9.19 - 12.90	6.50 - 12.90
Gender (n [%])					
Female			12 (71)	7 (88)	19 (76)
Male			5 (29)	1 (13)	6 (24)
Race (n [%])					
Caucasian			5 (29)	5 (63)	10 (40)
Black			12 (71)	3 (38)	15 (60)
Other			0 (0)	0 (0)	0 (0)
Height/Length (in)					
Mean (SD)			45.8 (7.3)	53.9 (7.4)	48.1 (8.1)
Median			48.0	56.0	49.5
Range			30 - 54	39 - 62	30 - 62
Weight (lb)					
Mean (SD)			58.1 (11.3)	100.3 (38.3)	71.6 (30.3)
Median			60.0	96.5	60.0
Range			40 - 79	53 - 165	40 - 165
Body Surface Area Involvement (%)					
Mean (SD)			45.7 (10.8)	41.9 (7.4)	44.5 (9.8)
Median			40.0	39.0	40.0
Range			[redacted]		
Overall Disease Status[a]					
Mean (SD)			2.0 (0.0)	2.3 (0.5)	2.1 (0.3)
Median			2.0	2.0	2.0
Clinical Signs/Symptoms Total Severity Index[b]					
Mean (SD)			9.8 (1.0)	11.4 (1.7)	10.3 (1.4)
Median			10.0	11.5	10.0
Range			[redacted]		
Treatment Area (n [%])					
Face[c]			0 (0)	0 (0)	0 (0)
Trunk and Extremities Only			17 (100)	8 (100)	25 (100)

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.**

Overall, 92% (23/25) of the subjects completed at least 14 days of treatment, while 68% (17/25) of subjects completed at least 21 days of treatment. The mean number of treatment days for all subjects was 19.3 with a range of 5 to 22 days. Because this study was terminated early in the enrollment phase, there were only two groups with subjects enrolled: the 6-8 year group and the 9-12 year group. The mean therapy durations for these respective age groups were 18.9 days and 20.1 days. The mean cumulative study drug use for all subjects was 79.4 grams. The minimum total amount of study drug applied by any one subject was 14.7 grams while the maximum total amount applied was 165.7 grams. The mean total drug usage for the 6- to 8-year group and the 9- to 12-year group was 82.3 grams and 73.2 grams, respectively. The mean weekly study drug use at days 1-7, days 8-14, and day ≥ 15 for all subjects was 32.4 grams, 33.6 grams, and 24.7 grams, respectively.

Reviewer's Comment: *All of the patients in the ITT population (25/25) are evaluable for local tolerance of Diprosone Lotion, 0.05%. However, for the evaluation of the hypothalamic-pituitary-adrenal axis, 8 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. . It also has been noted that patient 01/04 received the lower dose of Cortrosyn when she should have received the higher dose. 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
0001/000003	F/7yr 1mo/N	**4.78**[b]	**14.17**[c]	9.39
0001/00004	F/7yr 4mo/C	14.28	20.19	**5.91**[d]
0001/000010	F/7yr 2mo/C	11.49	**17.47**	**5.98**
0004/000006	F/11yr 3mo/N	**3.19**	19.97	16.78
0004/000007	F/8yr 9mo/C	11.49	**16.56**	**5.07**
0004/000009	F/12yr 10mo/C	15.88	22.40	**6.52**
0004/000010	F/7yr 9mo/N	**4.57**	20.77	16.20
0004/000012	M/7yr 10mo/N	**3.77**	**12.00**	8.23

[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 two (01/08 and 04/03) are excluded from the final analysis of HPA axis suppression. Subject 01/08 did not have any baseline testing of the HPA axis done and subject 04/03 did not have any endpoint (end-of-treatment) values for cortisol recorded. Table 3 lists these patients with their baseline demographics.*

Table 3
Additional Subject Exclusions

Center/Subject	Sex/Age/Race[a]
00001/000008	F/7yr 8mo/N
0004/0000003	F/9yr 2mo/C

[a] C=Caucasian N=nonCaucasian

7.1.1.4.2 Safety outcomes

There are 15 patients (15/25), 60% of the ITT population that are evaluable for HPA axis suppression. Eight patients are excluded because they exhibited suppression upon entry into the study, one because at the end of treatment, the Cortrosyn stimulation test was not administered and one because baseline Cortrosyn testing testing 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 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=15)	0	0	10	5
Cutaneous evaluation (N=25)	0	0	17	8

HPA Axis Evaluation Results

A total of 11 of the 15 evaluable patients (73%) 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 11 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=15)

Subject	Sex/Age/Race[a]	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	F/9yr 4mo/N	13.37	22.47	9.10	18.99	**10.37**[b]	**-8.82**[c]	*	*	*
01/02	F/11yr 3mo/N	18.77	28.60	9.83	7.97	**10.76**	**2.79**	13.59	26.10	12.51
01/05	F/7yr 7mo/N	12.98	23.27	10.29	**3.37**[d]	**10.47**	7.10	21.49	29.97	8.48
01/07	F/7yr 7mo/N	10.29	20.48	10.19	9.68	**16.56**	**6.88**	*	*	*
01/09	M/6yr 8mo/N	13.08	23.09	10.01	33.89	24.47	**-9.42**	*	*	*
01/11	F/6yr 6mo/N	10.18	18.59	8.41	10.98	**16.56**	**5.58**	13.77	25.08	11.31
04/01	F/8yr 6mo/N	14.17	23.27	9.10	**0.98**	**0.98**	**0.00**	13.48	**15.88**	**2.40**
04/08	M/9yr 5mo/C	10.29	21.67	11.38	6.89	**13.37**	**6.48**	*	*	*
04/11	F/10yr 1mo/C	10.47	25.08	14.61	**1.67**	**6.78**	**5.11**	6.78	20.59	13.81
04/13	M/7yr 11mo/C	9.39	27.58	18.19	9.97	**12.18**	**2.21**	*	*	*
04/14	M/6yr 10mo/N	7.39	19.79	12.40	7.58	**10.37**	**2.79**	7.47	**9.89**	**2.42**

[1]Adapted from table 1.1, attachment 1, volume 14.1, pgs. 216-217; a= N=non-Caucasian; C=Caucasian
#abnormal values are bolded b- should be >18 ug/dL; c- should be at least 7ug/dL; d- 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=0	2yr-5yr n=0	6yr-8yr n=10	9yr-12yr n=5
No. suppressed	0	0	7	4
%	0	0	70	80

Reviewer's Comment: *Tables 5 and 6 reveal that there is a significant amount of adrenal suppression with use of Diprosone Lotion, 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 70% in the 6 year to 8 year old group to 80% in the 9 year to 12 year old group. The study was aborted because the sponsor found rate-limiting safety of at least 10% suppression. Therefore, it is assumed that patients younger than 6 years of age will also experience HPA axis suppression using Diprosone Lotion, given the higher skin surface to body mass ratio in younger patients. Six of the 11 patients who demonstrated adrenal suppression (55%) had a follow-up Cortrosyn®*

stimulation test. Four of these 6 patients (67%) showed recovery of the hypothalamic pituitary adrenal axis. Unfortunately, there are no 2-week follow-up results for the remaining 5 patients (45%) 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 Lotion, 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. The results of this study were surprising, given Diprosone Lotion, 0.05% is classified as a Class V steroid, of medium potency. It suggests that the lotion vehicle may enhance the ability of the drug product, betamethasone dipropionate, to be systemically absorbed through the skin.

In the statistical review by Dr. Shiowjen Lee, statistical tests were not used as the numbers are too small. The relationship between HPA axis suppression and amount of drug used, %BSA involved, and weight were analyzed on a numerical basis. Subjects having HPA axis suppression used a numerically larger mean amount of drug (92.8 grams vs. 69.4 grams); they had a slightly higher %BSA involved (45.8% vs. 41.8%); and they had a numerically lower mean weight at Visits 1 and 4 (65 lbs. vs. 81 lbs. and 65 lbs. vs. 80 lbs., respectively). Differences with respect to age and number of days of treatment were miniscule(see statistical consult for full details).

Cutaneous Safety

The ITT population (N=25) was evaluable for cutaneous safety. During the treatment phase, local (cutaneous) adverse events were reported for three subjects. Moderate dry skin, assessed as possibly related to study medication, was reported for subject 01/11. Events of mild erythema and dry skin were reported for subject 04/11; and events of mild paresthesia, pruritus, and erythematous rash were reported for subject 04/08. Subject 01/02 had a mild case skin atrophy (loss of normal skin markings) at visit 4, which resolved on follow-up. No patients in this study applied study medication to the face.

During the follow-up phases of the study, two subjects reported local adverse events of pruritus, subject 01/11 and subject 01/08, who reported the symptom to be of mild and moderate intensity, respectively.

Laboratory Safety

There were 2 subjects with clinically meaningful abnormalities in the study. Subject 01/03 exhibited a clinically meaningful increase in WBCs in the urine (25 HPF, normal range = 0-5) on day 22. Subject 04/05 exhibited a clinically meaningful increase in RBCs in the urine (9 HPF, normal range = 0-2) on day 22. Both patients had normal values at baseline. No tests were done at follow-up.

Reviewer's Comment: *Under investigator's comments, there were not any comments regarding these laboratory results. In this reviewer's opinion, topical corticosteroids are not known to*

cause either hematuria or pyuria, therefore, these events are most likely not attributable to Diprolene AF Cream, 0.05%.

8 Safety Conclusions

This study clearly demonstrates that Diprosone Lotion, 0.05% has a poor safety profile in pediatric patients. The primary systemic safety factor, HPA axis suppression, occurred in almost all of the evaluable pediatric patient in the age groups enrolled, ages 6-12 years old after treatment with Diprosone Lotion, 0.05%. This range of suppression is from 80% in 9-12 year olds, to 70% in 6-8 year olds. It can be extrapolated that pediatric patients younger than 6 years of age would demonstrate a similar poor safety profile with use of Diprosone Lotion. The secondary safety variable of cutaneous atrophy revealed a 4% incidence of cutaneous atrophy, which was mild and in one subject. Other cutaneous safety findings of dry skin, pruritus, and erythema, which ranged from 4-8%, is not an unusual finding for this drug product in a lotion vehicle.

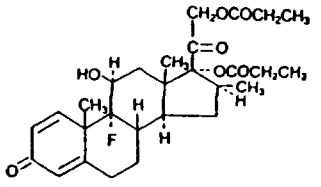
9 Labeling Review

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 Lotion 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 Lotion 0.05% w/w contains: 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone) in a lotion base of isopropyl alcohol, USP (39.25%) and purified water, USP; slightly thickened with carbomer 974P; the pH is adjusted to approximately 4.7 with sodium hydroxide.

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.

Twenty-five pediatric patients ages 6 to 12 years, with atopic dermatitis, were enrolled in an open-label, hypothalamic-pituitary-adrenal (HPA) axis safety study. DIPROSONE Lotion was applied twice daily for 2 to 3 weeks over a mean body surface area of 45% (range 35% to 72%).

patients, adrenal suppression was indicated by either a ≤ 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.

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

9.3 Indications and Usage

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

9.4 Contraindications

CONTRAINDICATIONS DIPROSONE Lotion is contraindicated 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 11 subjects who showed evidence of suppression, 6 subjects were tested 2 weeks after discontinuation of Diprosone Lotion, 0.05% and 4 of the 6 (67%) 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

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.

[redacted]

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 [redacted]

9.5.5 Pregnancy

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

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

[redacted]

In an open-label study, 11 of 15 (73%) pediatric patients (aged 6 years - 12 years old) using Diprosone Lotion for treatment of atopic dermatitis for 2 to 3 weeks demonstrated [redacted] suppression. (See **CLINICAL PHARMACOLOGY - Pharmacokinetics.**)[1,2]

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.

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 Lotion 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 Lotion during a pediatric study include: paresthesia (burning), erythema, erythematous rash, and dry skin. These adverse reactions each occurred in a different patient; 4% of the 25 patient population, respectively. An adverse reaction reported to be possibly or probably related to treatment in 2 different patients, 8%, of the 25 patients is puritis.[5]

9.7 Overdosage

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

9.8 Dosage and Administration

DOSAGE AND ADMINISTRATION [redacted]

[redacted]

Apply a few drops of DIPROSONE Lotion to the affected area and massage lightly until it disappears. Apply twice daily, in the morning and at night. For the most effective and economical use, apply nozzle very close to affected area and gently squeeze bottle.

DIPROSONE Lotion is not to be used with occlusive dressings.

9.9 How Supplied

HOW SUPPLIED DIPROSONE Lotion 0.05% w/w is available in 20-mL (18.7-g) (NDC 0085-0028-04) and 60-mL (56.2-g) (NDC 0085-0028-06) plastic squeeze bottles; boxes of one.
Protect from light. Store in carton until contents are used.

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

Schering Corporation
Kenilworth, NJ 07033 USA

Rev[redacted] 5/01
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10 Recommendations

It is recommended that Diprosone Lotion, 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. Additional provider educational material should be considered by the sponsor.

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
In DFS 7/18/01

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