

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-555/S-008

19-555/S-016

MEDICAL REVIEW

Medical Officer's Review of NDA 19-555
Efficacy Supplement

NDA#: 19-555
Serial#: SE5-016
HFD#1: 006888

HFD#2: 018185

Submission date: 10/4/00
CDER Stamp date: 10/5/00
CDER Stamp date-Revised data analysis
6/1/01
Review began: 10/10/00
Review completed: 07/17/01

Sponsor: Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Generic name: Betamethasone dipropionate

Trade name: Diprolene AF Cream. 0.05%

Pharmacologic Category: Anti-inflammatory

Indication(s): Corticosteroid responsive dermatoses

Dosage Form(s): Cream

Route (s) of Administration: Topical

Related Drugs: Diprosone Cream – NDA 17-536
Diprosone Lotion – NDA 17-781
Diprosone Ointment – NDA 17-691

Related Review: Statistics – 6/20/01 (draft)

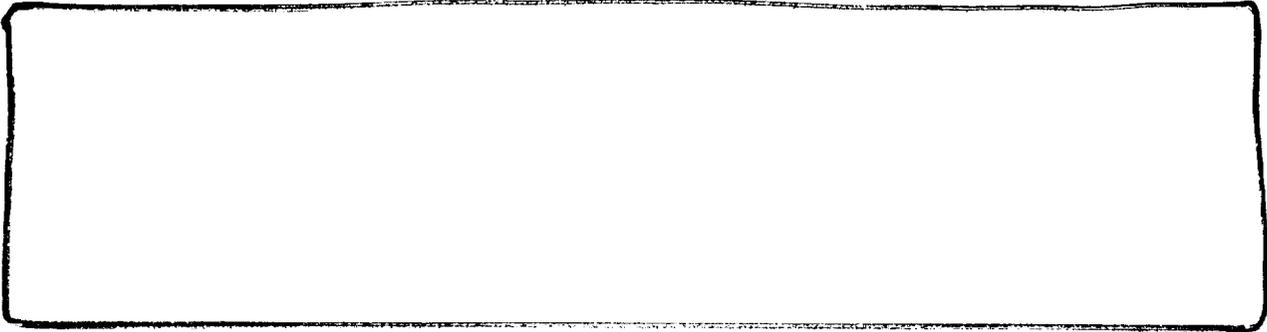
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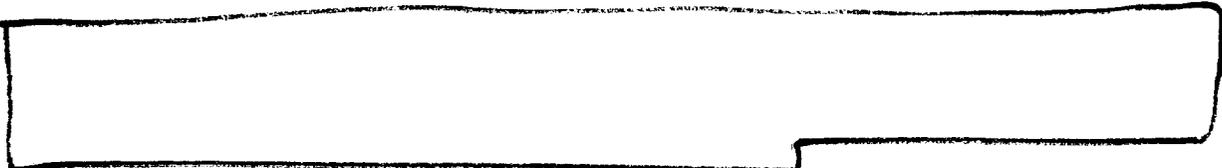
5.3 Proposed Information for patients



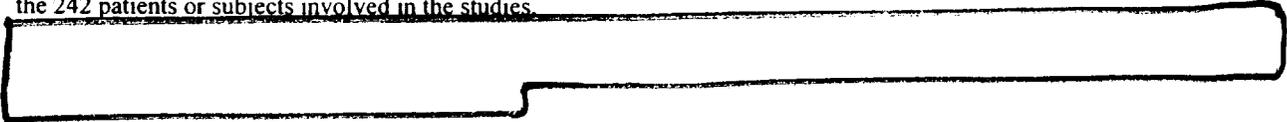
5.4 Proposed Pediatric Use Section



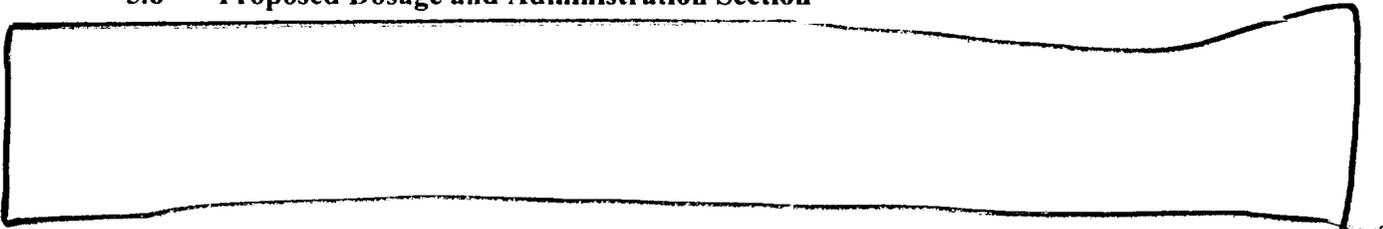
5.5 Proposed Adverse Reaction Section



ADVERSE REACTIONS The only local adverse reaction reported to be possibly or probably related to treatment with DIPROLENE AF Cream during adult controlled clinical studies was stinging. It occurred in 1 patient, 0.4%, of the 242 patients or subjects involved in the studies.



5.6 Proposed Dosage and Administration Section



6 Description of Clinical Source

Study PO1260 – This is an open-label, multicenter, safety study of Diprolene AF Cream, 0.05% conducted in response to a pediatric written request. The study was to evaluate the systemic and cutaneous safety of Diprolene AF 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 25, 2000 to September 5, 2000 in which 67 subjects were

enrolled. Efficacy was not requested as the efficacy of this drug product in adults can be extrapolated to pediatric patients.

7 Clinical Study

7.1 Sponsor's protocol # - PO1260

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

7.1.1 Investigators

- | | |
|----------------------------------|-----------------------|
| 1. Lawrence F. Eichenfield, M.D. | 01/San Diego, CA |
| 2. Issac Willis, M.D. | 02/Atlanta, GA |
| 3. Jon Hanifin, M.D. | 04/Portland, OR |
| 4. John DiGiovanna, M.D. | 05/Providence, RI |
| 5. Leonard Swinyer, M.D. | 06/Salt Lake City, UT |
| 6. Libby Edwards, M.D. | 07/Charlotte, NC |

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 Diprolene AF 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

Subjects requiring treatment applications of more than 45 g of Diprolene AF cream per week

Study Plan: Subjects were to apply the medication to the affected areas of the body bid (not to exceed 45g per week). 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 post-stimulation was defined as either a 7 µg/100 ml incremental rise in plasma cortisol or a plasma 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 weighing ≥ 15 kg would receive a Cortrosyn dose of 0.25 mg and subjects weighing < 15 kg would receive a dose of 0.125 mg of Cortrosyn. 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.

A total of 67 subjects at six of seven sites were enrolled in the study and treated with study medication the same day. One site did not enroll any subjects. All subjects had moderate to severe atopic dermatitis. The age range (all age groups) for this study was 1.20 years to 12.99 years. There was a similar percentage of females and males (51% and 49%, respectively; 46% of the subjects were Caucasian and 36% were Black. The mean percent (all age groups) of BSA disease involvement was 58% (range 35% to 95%). The percentage and number of subjects whose treated areas included the face was 34 (51%); whereas, the treated areas for 33 subjects (49%) involved the trunk and extremities only. See table 1 for full baseline demographics.

Table 1
Summary of Demographic Data
ITT Population

Demographic Characteristic	Age Group				Total (n=67)
	3 mo – 1 yr (n=5)	2 yr – 5 yr (n=18)	6 yr – 8 yr (n=30)	9 yr – 12 yr (n=14)	
Age (yr)					
Mean (SD)	1.40 (0.17)	4.40 (1.14)	7.39 (0.79)	10.78 (1.03)	6.85 (2.85)
Median	1.35	4.29	7.46	10.96	7.01
Range	1.20 - 1.60	2.37 - 5.99	6.00 - 8.90	9.03 - 12.99	1.20 - 12.99
Gender (n [%])					
Female	3 (60)	12 (67)	14 (47)	5 (36)	34 (51)
Male	2 (40)	6 (33)	16 (53)	9 (64)	33 (49)
Race (n [%])					
Caucasian	2 (40)	12 (67)	11 (37)	6 (43)	31 (46)
Black	1 (20)	3 (17)	14 (47)	6 (43)	24 (36)
Other	2 (40)	3 (17)	5 (17)	2 (14)	12 (18)
Height/Length (in)					
Mean (SD)	29.6 (2.5)	41.1 (3.4)	48.3 (3.7)	55.3 (4.2)	46.5 (7.8)
Median	31.0	40.8	49.0	56.2	47.0
Range	26 - 32	34 - 47	42 - 55	47 - 60	26 - 60
Weight (lb)					
Mean (SD)	23.4 (2.6)	40.2 (9.1)	59.5 (14.9)	85.1 (21.1)	57.0 (23.2)
Median	22.0	40.0	56.6	82.5	55.0
Range	22 - 28	25 - 62	39 - 93	55 - 134	22 - 134
Body Surface Area Involvement (%)					
Mean (SD)	69.0 (15.2)	64.4 (20.3)	56.3 (16.8)	50.9 (15.5)	58.3 (18.0)
Median	70.0	60.0	57.5	45.0	56.0
Range					
Overall Disease Status^a					
Mean (SD)	2.4 (0.5)	2.3 (0.5)	2.1 (0.3)	2.2 (0.4)	2.2 (0.4)
Median	2.0	2.0	2.0	2.0	2.0
Clinical Signs/Symptoms Total Severity Index^b					
Mean (SD)	13.0 (3.4)	11.8 (2.9)	12.2 (2.0)	13.1 (2.4)	12.3 (2.4)
Median	12.0	11.0	12.0	12.0	12.0
Range					
Treatment Area (n [%])					
Face ^c	2 (40)	10 (56)	17 (57)	5 (36)	34 (51)
Trunk and Extremities Only	3 (60)	8 (44)	13 (43)	9 (64)	33 (49)

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 67 subjects, 64 (96%) completed the full 3-week treatment phase. Three subjects (4%) discontinued treatment prior to completing the 3-week treatment regimen: one because of clearing of atopic dermatitis following 2 weeks of treatment and two subjects for other reasons (one of these two subjects did not complete any follow-up visit). Ten subjects (15%) discontinued the study after completing the 2-week follow-up visit. Number of days of treatment for these subjects ranged from 12-23 days. There were six subjects (9%) who discontinued the study without completing any follow-up visit. Number of days of treatment for these subjects ranged from 17 to 22 days. There were 19 subjects (28%) who completed both the 2-week and 4-week follow-up visits.

Reviewer's Comment: Patient 07/02 was a 19 month old who is not evaluable because the post cortosyn blood sample was reported as QNS (quantity not sufficient). She, therefore, cannot be included in the total evaluable patients for systemic safety assessment. She was also the patient who did not return for follow-up. The six subjects that did not show up for follow-up visits, did, however, have HPA axis suppression testing at endpoint.

Overall, 99% (66/67) of subjects completed at least 14 days of treatment, while 88% (59/67) of subjects completed at least 21 days of treatment. The mean number of treatment days for all subjects was 21.1 with a range of 12 to 27 days. The mean cumulative study drug use for all subjects was 55.9 grams. The minimum total amount of study drug applied by any one subject was 9.8 grams, while the maximum total amount applied was 122.6 grams. Across the four age groups, mean total drug usage ranged from 43.0 grams (3-month to 1-year group) to 64.7 grams (9 – 12-year group). The mean weekly study drug use at days 1-7, days 8-14, and \geq day 15 for all subjects was 22.5 g, 18.7 g, and 18.8 g, respectively.

Reviewer's Comments: All of the patients in the ITT population (67/67) are evaluable for local tolerance of Diprolene AF Cream, 0.05%, as a minimum of 12 days of treatment with the drug product was completed. However, for the evaluation of the hypothalamic-pituitary-adrenal axis, 6 patients will be excluded from the evaluation, as a major protocol violation occurred. According to Cortosyn[®] labeling, these patients ~~exhibited varying degrees of adrenal suppression~~ 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.

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Table 2
Patients with Baseline Adrenal Suppression

Center/Subject	Sex/Age/Race ^a	Serum Cortisol Concentration (µg/dL) [*]		
		Baseline		
		Pre	Post	Stim Change
0001/000018	F/2yr 8mo/N	4.28^b	25.48 ^c	21.20 ^d
0002/000005	F/11yr 30dy/N	19.06	24.86	5.80
0002/000010	F/11yr 4mo/N	3.48	19.06	15.58
0002/000016	F/6yr 11mo/N	2.79	27.08	24.29
0007/000003	F/4yr 3mo/C	6.20	10.18	3.98
0007/000005	M/7yr 11mo/N	21.67	28.38	6.71

^aC=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

7.1.1.4.3 Safety outcomes

There are 60 patients (60/67), 90% of the ITT population that are evaluable for HPA axis suppression. Six patients are excluded because they exhibited suppression upon entry into the study and one because at the end of treatment, the post-cortrosyn cortisol value 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=60)	4	16	28	12
Cutaneous evaluation (N=67)	5	18	30	14

HPA Axis Evaluation Results

A total of 19 of the 60 evaluable patients (32%) 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 19 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 Endpoint¹
Evaluable Patients (N=60)

Center/ 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
01/000004	M/11yr 2mo	8.19	22.58	14.39	1.78	20.48	18.70	*	*	*
01/000007	F/6yr 1dy	9.89	24.28	14.39	15.98	21.67	5.69	*	*	*
01/000008	F/6yr 4mo	6.78	24.57	17.79	14.50	20.77	6.27	*	*	*
01/000014	F/1yr 6mo	16.56	25.99	9.43	14.39	19.90	5.51	*	*	*
01/000016	M/4yr 3mo	7.87	22.58	14.71	6.89	17.18	10.29	*	*	*
02/000003	F/7yr 9mo	7.79	28.09	20.30	3.88	25.19	21.31	*	*	*
02/000018	M/8yr 7mo	6.27	19.06	12.79	5.69	17.58	11.89	*	*	*
02/000019	F/6yr 6mo	11.67	24.79	13.12	*	*	*	4.97	20.37	15.40
04/000003	M/5yr 8mo	7.68	20.30	12.62	5.18	13.27	8.09	*	*	*
04/000009	M/1yr 3mo	12.18	22.69	10.51	7.07	14.57	7.50	*	*	*
05/000001	M/7yr 5mo	11.49	24.68	13.19	7.97	15.88	7.91	*	*	*
05/000002	F/7yr 7mo	8.19	24.28	16.09	18.67	17.47	-1.20	8.48	21.38	12.90
05/000003	M/6yr 5mo	18.67	27.69	9.02	17.40	23.89	6.49	*	*	*
06/000003	M/10yr 7mo	10.87	23.6	12.73	12.29	17.69	5.40	*	*	*
07/000001	F/4yr 10mo	7.29	24.18	16.89	0.98	10.29	9.31	9.68	21.67	11.99
07/000009	M/5yr 6mo	8.49	25.70	17.22	5.87	14.50	8.63	*	*	*
07/000010	F/7yr 9mo	9.97	22.18	12.21	10.87	14.97	4.10	10.47	20.70	10.23
07/000011	F/3yr 7mo	14.10	29.79	15.69	15.98	22.29	6.31	*	*	*
07/000012	F/4yr 6mo	6.49	22.80	16.31	3.19	8.99	5.80	7.18	21.67	14.49

¹Adapted from table 1.1, attachment 1, volume 14.1, pg. 213

[#]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=4	2yr-5yr n=16	6yr-8yr n=28	9yr-12yr n=12
No. suppressed	2	6	9	2
%	50	38	32	17

Reviewer's Comment: Tables 4 and 5 reveal that there is a significant amount of adrenal suppression with use of Diprolene AF cream, 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 50% in the 3 month-1 year old group. Five of the 19

patients (26%) had a follow-up Cortrosyn[®] stimulation test. Four of these patients (21%) showed recovery of the adrenal axis. One patient (02/000019), a 6 year old, did not have cortrosyn stimulation at endpoint but at the 2-week follow-up still showed mild suppression of the adrenal gland with a basal output of 4.97 µg/dL. One can infer from this result that the subject's adrenal gland was suppressed at endpoint and the 2-week post-treatment result showed a slowly recovering adrenal gland. Unfortunately, there are no 2-week follow-up results for the remaining 12 patients (63%) who exhibited evidence of suppression. It might be surmised that since 4 of the 5 (80%) 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 certainty 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 Diprolene AF 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.

Table 6 shows the amount of drug used by each of the subjects who experienced adrenal suppression. None of these patients used the drug outside of the labeled conditions. Only one patient (who did not exhibit adrenal suppression) used more than the maximum of 45 grams in one week. This was patient 01/000018 who used 46.2 grams the first week.

Table 6
Amount of Drug Used by Endpoint
Subjects with HPA Axis Suppression

Center/Subject	Amount of Drug Used (Gms)
01/000004	42.1
01/000007	35.7
01/000008	106.3
01/000014	38.0
01/000016	88.9
02/000003	48.7
02/000018	21.5
02/000019	22.5
04/000003	66.1
04/000009	73.2
05/000001	106.2
05/000002	39.0
05/000003	30.0
06/000003	96.8
07/000001	108.5
07/000009	48.3
07/000010	37.4
07/000011	29.8
07/000012	77.5

Reviewer's Comment: Analysis of the data by Dr. Shiojwen Lee of biostatistics, did not reveal a relationship between amount of study drug used, body weight, age, or sex and the incidence of HPA axis suppression. There was, however, a statistical relationship between the amount of body surface area involved and the risk of developing HPA axis suppression. According to Dr. Lee's analysis, "for an increase of 1% of body surface area involved, there is an increase in the odds of the presence of HPA suppression by 4.4%." The p value for this is ≤ 0.01 (see statistical consult for full details). From a medical viewpoint, the fact that BSA could make a difference in the absence of a correlation with amount of study medication used, may be related to the increased body surface area to body mass ratio in young children and infants.

Cutaneous Safety

Reviewer's Comment: According to the sponsor, "One subject (1%) experienced adverse events during the treatment phase of the study that were considered to be possibly related to treatment. Subject PO1260-07/11 experienced signs of skin atrophy (telangiectasia) that increased from mild to moderate as well as signs of mild overt atrophy following 22 days of treatment. The events were ongoing at the end of 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, "...signs of skin atrophy (telangiectasia, shininess, and bruising) were observed in 6% of the subjects (ages 1 to 12 years) during treatment and immediately following cessation of treatment. Overt atrophy was observed in 3% of the subjects during treatment and immediately following cessation of treatment."

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

The ITT population (N=67) was evaluable for cutaneous safety (refer to table 3, pg). Clear-cut treatment emergent cutaneous atrophy, whether viewed with 2x magnification or with the naked eye occurred in 7 of the 67 patients (10%) treated with Diprolene AF Cream, 0.05%. From the data provided, it appears that 34 patients applied the drug product to some part of the face. Two of these patients developed telangiectasias in the face. Other patients developed telangiectasias on the face but the investigators stated in those cases that the drug product had not been applied to that particular part of the face. Patient 01/13, a 3 year old, was first noted to have mild telangiectasias at visit 3 that was still noted at the end of study (4 weeks post- treatment). Patient 07/09, a 5-year-old, was first noted to have moderate telangiectasia with overt atrophy at visit 4 that had not resolved by the end of the study. Subject 07/11 was a 3-year-old who progressed from mild telangiectasia at baseline (with no overt atrophy) to moderate telangiectasia at visit 4 (with overt atrophy). Investigator comments that this patient had "eczema" only at the hairline of the face and mother adamantly denied applying study medication to the cheeks, where the telangiectasia were observed. Although, it is suspect that there may have been some transference of medication, it is not certain, so this patient cannot be included in a clear-cut case of treatment emergent cutaneous atrophy.

Five different subjects (8%) experienced varying degrees of atrophy in areas other than the face (trunk and/or extremities) that were treatment emergent (absent at baseline but development during the course or after treatment). There was mild shininess in a 4 year old,

mild bruising in a 6 year old, moderate shininess in a 1 year old, moderate bruising in a 9 year old, and mild bruising in an 11 year old. Unlike the facial area, signs of atrophy in the non-facial areas all resolved upon discontinuation of the medication by week four or five. Table 7 is a summary of the cutaneous effects by age group of Diprolene AF Cream, 0.05% when used as labeled for 2 – 3 weeks.

Table 7
Summary of Cutaneous Atrophy
ITT Population

Cutaneous Atrophy	Age Group			
	3 months- 1 year N ¹ =5 (%)	2 years-5 years N ¹ =18 (%)	6 years – 8 years N ¹ =30 (%)	9 years- 12 years N ¹ =14 (%)
Facial	0/2 (0)	2/10 (20)	0/17 (0)	0/5 (0)
Non-Facial	1 (20)	1 (6)	1 (3)	2 (14)
Total	1 (20)	3 (17)	1(3)	2 (14)

¹This is the denominator unless otherwise noted.

In this reviewer’s opinion, Diprolene AF Cream, 0.05% demonstrates the ability to cause cutaneous atrophy in a significant proportion of the pediatric population. All age groups reached rate-limiting safety as defined by the sponsor. It is important to note that the risk is particularly high and unacceptable in children 2 – 5 years and 3 months – 1 year old (20% and 17%, respectively). The results in facial skin show that it (the face) is particularly vulnerable, and in fact, may not be reversible as each patient continued to have atrophy 2-4 weeks post-treatment. Both methods of detecting cutaneous atrophy, with 2x magnification or the unaided eye, are of clinical significance, as this drug product would probably be used chronically in a remitting and relapsing disease such as atopic dermatitis.

Other cutaneous events included one case of skin burn and 2 cases of mild urticaria that occurred during the treatment phase. Patients did not discontinue because of these events.

Laboratory Results

There were 23 subjects that exhibited a clinically meaningful lab result. Subject 02/15, a 7 year old male, had an increase in RBCs in the urine (11 HPF, normal range = 0-2) on day 22, 1 day after the last application of study medication. Baseline value for RBCs in the urine was also elevated (8 HPF). There was no retest conducted at follow-up. Subject 05/02, a 7 year old female, exhibited an increase in WBCs in urine (17 HPF, normal range = 0-5) on day 15, one day after the last application of study medication. This subject’s baseline value was normal. There was no retest during the follow-up phase.

At visit 4 (day 22), subject 02/14, a 6 year old female, exhibited severe anemia. The subjects hemoglobin had decreased from 133 g/L at baseline to 99 g/L (normal range = 114 to 151 g/L). The subject’s hematocrit had also decreased from 0.39 to 0.32 V/V (normal range = 0.36 to 0.47 V/V) over the same period. Although several attempts were made to have the subject return for follow-up, patient never returned.

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%. Regarding subject 02/14 with the anemia, although within the normal range, the patient also had a decrease in the erythrocyte count from 4.9 m/mm³ to 4.4 m/mm³ (normal range = 4.2 to 5.3 m/mm³) and a decrease in the leukocyte count from 5.4 k/mm³ to 4.9 k/mm³ (normal range = 4.0 to 10.5 m/mm³). Her platelet count remained the same. These changes are not likely due to topically applied betamethasone dipropionate.

8 Safety Conclusions

This study clearly demonstrates that Diprolene AF 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 3 months – 12 years old after treatment with Diprolene AF Cream, 0.05% under labeled conditions for atopic dermatitis. This range of suppression is from 17% in 9-12 year olds, to 50% in infants 3 months – 1 year old. The secondary safety variable of cutaneous atrophy revealed a 10% overall incidence of cutaneous atrophy. Furthermore, the drug product should not be used on the face for 20% of those patients developed atrophy that persisted beyond study endpoint.

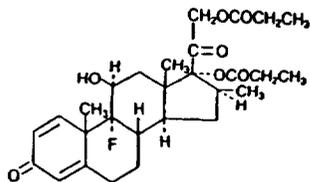
9 Labeling Review

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 DIPROLENE® AF Cream contains betamethasone dipropionate, USP, a synthetic adrenocorticosteroid, for dermatologic use in an emollient base. Betamethasone, an analog of prednisolone, has a high degree of corticosteroid activity and a slight degree of mineralocorticoid activity. Betamethasone dipropionate is the 17, 21-dipropionate ester of betamethasone.

Chemically, betamethasone dipropionate is 9-fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17,21-dipropionate, with the empirical formula C₂₈H₃₇FO₇, 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 DIPROLENE AF Cream 0.05% contains: 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone) in an emollient cream base of purified water, USP; chlorocresol; propylene glycol, USP; white petrolatum, USP; white wax, NF; cyclomethicone; sorbitol solution, USP; glyceryl oleate/propylene glycol; cetareth-30; carbomer 940, NF; and sodium hydroxide R.

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** section.)

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

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

DIPROLENE AF Cream was applied once daily at 7 grams per day for 1 week to diseased skin, in adult patients with psoriasis or atopic dermatitis, to study its effects on the hypothalamic-pituitary-adrenal (HPA) axis. The results suggested that the drug caused a slight lowering of adrenal corticosteroid secretion, although in no case did plasma cortisol levels go below the lower limit of the normal range.

Sixty-seven pediatric patients ages 1 to 12 years, with atopic dermatitis, were enrolled in an open-label, hypothalamic-pituitary-adrenal (HPA) axis safety study. DIPROLENE AF Cream was applied twice daily for 2 to 3 weeks over a mean body surface area of 58% (range 35% to 95%).

[REDACTED]

In 019 of 060 evaluable (032%) patients, adrenal suppression was indicated by either a \leq 5 mcg/dL pre-stimulation cortisol, or a cosyntropin post-stimulation cortisol \leq 18 mcg/dL and/or an increase of \leq 7 mcg/dL from the baseline cortisol.

[REDACTED]

Studies performed with DIPROLENE AF Cream 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 DIPROLENE AF Cream is a high-potency corticosteroid³ indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-

responsive dermatoses.

9.4 Contraindications

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

PRECAUTIONS General: Systemic absorption of topical corticosteroids has produced reversible 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 corticosteroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. (See **DOSAGE AND ADMINISTRATION** section.)

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 19 who showed evidence of suppression, 4 patients were tested 2 weeks after discontinuation of DIPROLENE AF Cream, and 3 of the 4 had complete recovery of HPA axis function. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

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

1. This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. 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** section.)
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 [REDACTED]

[REDACTED]

9.5.5 Pregnancy

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

[REDACTED]

9.5.6 Labor and delivery

9.5.7 Nursing mothers

Nursing Mothers: It is not known whether topical administration of corticosteroids can 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

9.5.8 Pediatric use

Pediatric Use: [REDACTED]

Use of

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

In an open-label study, 19 of 60 (32%) pediatric patients (aged 3 months – 12 years old) using DIPROLENE AF Cream for treatment of atopic dermatitis demonstrated physiologic HPA axis suppression. The proportion of patients with HPA axis suppression in this study was progressively greater the younger the age group (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. The study described above supports this premise, as suppression in 9-12 year olds, 6-8 year olds, 2-5 year olds, and 3 months-1 year old was 17%, 32%, 38%, and 50%, respectively.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children 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. Chronic corticosteroid therapy may interfere with the growth and development of children.

9.6 Adverse Reactions

ADVERSE REACTIONS The only local adverse reaction reported to be possibly or probably related to treatment with DIPROLENE AF Cream during adult controlled

clinical studies was stinging. It occurred in 1 patient, 0.4%, of the 242 patients or subjects involved in the studies.

Adverse reactions reported to be possibly or probably related to treatment with DIPROLENE AF Cream during a pediatric clinical study include signs of skin atrophy (telangiectasia, bruising, shininess). Skin atrophy occurred in 7 of 6 patients [redacted] involving all ages [redacted] from 3 months – 12 years of age.⁶

The following local adverse reactions are reported infrequently when topical corticosteroids are used as recommended. These 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.

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

Apply a thin film of DIPROLENE AF Cream to the affected skin areas once or twice daily. Treatment with DIPROLENE AF Cream should be limited to 45 g per week.

DIPROLENE AF Cream is not to be used with occlusive dressings.

9.9 How Supplied

HOW SUPPLIED DIPROLENE AF Cream 0.05% is supplied in 15-g (NDC 0085-0517-01) and 50-g (NDC 0085-0517-04) tubes; boxes of one.

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

Schering Corporation

Kenilworth, NJ 07033 USA

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10 Recommendation

It is recommended that Diprolene Cream AF, 0.05% continue not to be recommended 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.
Medical Officer, Dermatology

cc: HFD-540
HFD-340
HFD-540/CSO/CintronO
HFD-540/CHEM/Pappas
HFD-540/PHARM/BrownP
HFD-540/MO/Cook
HFD-880/Biopharm/Bashaw
HFD-725/Stats/LeeS
Draft 6/20/01
In DFS 7/18/01

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