CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-691/S-019

17-691/S-024

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Betamethasone dipropionate
NDA 17-536 S-024 (Diprosone Cream 0.05%)
NDA 17-691 S-024 (Diprosone Oint. 0.05%)
NDA 17-781 S-022 (Diprosone Lotion 0.05%)
NDA 19-555 S-016 (Diprolene AF Cream 0.05%)
Reviewer: E.D. Bashaw, Pharm.D.

Schering Corporation
Kenilworth, NJ 07033

Submission Date
May 31, 2001

Review of Multiple Pediatric Study Reports

Background

These four pediatric supplements are being reviewed together as these supplements are in response to a single pediatric written request. In addition they all relate, ultimately, to a single design in vivo HPA axis suppression study in which all four products were evaluated in the target population (pediatric patients between the age of 3 mos and 12 yrs. with corticosteroid responsive dermatoses).

Study Title: Phase IV multicenter, open label safety studies (four protocols combined) in pediatric patients with atopic dermatitis, treated with betamethasone diproprionate 0.05% formulations (Diprolene AF Cream, Diprosone Ointment, Diprosone Cream, and Diprosone Lotion) twice daily.

Study Design

Although reported out in a single report, this report actually covers four separate studies that utilize similar design features. Specifically the studies were designed to incorporate elements cited in the FDA written request. These can be summarized as follows:

- A minimum of 50 evaluable pediatric patients treated for 2 to 3 weeks with one of the four topical formulations (a total of 200 patients in the four studies);
- 30 of the 50 patients per study in the 6- to 8-year-old age range;
- If there were no rate-limiting safety factors occurring in the 6- to 8-year-old age range, continued enrollment of patients at progressively lower ages until a rate-limiting safety factor was found, or down to the age of 3 months if no safety factor was found;
- Frequent monitoring for cutaneous adverse events, and interruption or discontinuation of study medication for cutaneous adverse events;
- Body surface area with disease involvement of >35%;
- Completion of a 2-week post-treatment follow-up;

- Standard descriptive statistics performed for adverse events, laboratory values, and other safety measures, and a subgroup analysis for use of topical betamethasone dipropionate on the face.

"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 patients within any one of the age groups.
- Presence of overt atrophy in 5% (or greater) of patients in any one age group.
- Development of treatment-emergent adverse events of moderate or greater severity in 10% (or greater) of patients in any one age group.
- Presence of any of the individual signs of atrophy of moderate or greater severity in 5% (or greater) of patients in any one age group.
- Presence of striae of any degree in any patient in any one age group.

The trial was designed such that initially 10 patients aged >8 and up to 12 yrs were studied first, followed by 30 patients aged >6 and up to 8yrs, five patients >2 and up to 6yrs, and five patients 3 months up to 2years of age. Prior to going down to the next younger cohort, the results of clinical examination and HPA axis testing was to be completed in the previous cohort. Within a cohort, subset analysis for trends in toxicity were done after each 5 patients completed the trial. Summarized below is the patient age distribution from this trial.

Age Distribution
(planned number of patients per group)

Treatment Group	3mo to 1yr. (5)	2yr to 5yr (5)	6yr to 8yr (30)	9yr to 12yr (10)	Totals
Diprolene AF Cream	5	18	30	14	67
Diprosone Ointment	14	28	27	11	80
Diprosone Cream	7	27	20	9	63
Diprosone Lotion	0	0	17	8	25
Totals	26	73	94	42	235

The study population (all treated patients, ITT) age range included 6 months to 12 years. All patients were treated with one of four treatments twice daily for up to 3 weeks. Overall, 114 patients were female, 121 were male, and 111 were caucasian. A total of 196 patients (83%) completed 3 weeks of treatment and completed the 2-week follow-up period.

Cortrosyn® Challenge

HPA axis testing was conducted on day 1, and on either day 14 or 22. This was done so that those patients who cleared at two weeks could complete the trial without having to be exposed to an additional week of unnecessary dosing. Testing was done in accordance to the general directions as contained in the Cortrosyn® package insert. . Blood was collected prior to and 30min after administration of 250mcg of Cortrosyn®. The resulting blood samples were analyzed for cortisol and the results are summarized below by formulation, but not by age.

	Baseline		
Treatment Group	Pre-Dose (>5ug/dL)*	30min Post Dose (>18ug/dL)*	Pre-Post Difference (≥7ug/dL)*
Diprolene AF Cream	51(94%)**	54(100%)	52(96%)
Diprosone Ointment	59(92%)	57(89%)	56(88%)
Diprosone Cream	43(96%)	40(89%)	43(96%)
Diprosone Lotion	13(81%)	13(81%)	13(81%)

	Day 14		
Treatment Group	Pre-Dose (>5ug/dL)*	30min Post Dose (>18ug/dL)*	Pre-Post Difference (≥7ug/dL)*
Diprolene AF Cream	50(93%)**	44(81%)	45(83%)
Diprosone Ointment	60(94%)	49(77%)	49(77%)
Diprosone Cream	40(87%)	38(83%)	36(78%)
Diprosone Lotion	12(75%)	5(31%)	7(44%)

*Criteria for lack of HPA axis suppression

**Data represents the number of patients and (percentage) with detectable HPA axis suppression

Because of the involved nature of the data, the individual treatment by age group analysis is attached as Tables I-IV.

Examination of the data suggests that all formulations of betamethasone dipropionate can cause some degree of HPA axis suppression. In Study P01260 (Diprolene AF), there was little evidence of clinically relevant HPA-axis suppression based on cortisol response to Cortrosyn® stimulation; however, all four studies were terminated early for rate-limiting safety events associated with abnormal cortisol values. Of particular concern is the lotion product, which shows after a two-week treatment regimen a 69% failure rate to achieve an adequate cortisol stimulation response.

Rate Limiting Safety:

Criteria for rate-limiting safety in four areas (abnormal cortisol levels, adverse events, overt atrophy, and skin atrophy) were met for certain age groups in all four studies. The age groups and categories in which patients met these criteria are as follows:

Study P01260 (Diprolene AF Cream) –
abnormal cortisol concentration levels: 2 to 5 years, 6 to 8 years. 9 to 12 years;
treatment-emergent adverse events: 2 to 5 years, 9 to 12 years:
overt atrophy: 2 to 5 years:
signs of skin atrophy: 3 months to 1 year, 2 to 5 years, 9 to 12 years.

Study P01261 (Diprosone Ointment) –
abnormal cortisol concentration levels: 6 to 8 years;
treatment emergent adverse events: 3 months to 1 yr, 2 to 5 yts, 6 to 8 yrs, 9 to 12yrs;
signs of skin atrophy: 2 to 5 years.

Study P01262 (Diprosone Cream) –
abnormal cortisol concentration levels: 2 to 5 years, 6 to 8 years, 9 to 12 years;
treatment-emergent adverse events: 3 months to 1 year;
signs of skin atrophy: 6 to 8 years.

Study P01263 (Diprosone Lotion) –
(no patients were enrolled in the 3-month to 1 -year or 2to 5-year age groups)
abnormal cortisol concentration levels: 6 to 8 years, 9 to 12 years;
treatment-emergent adverse events: 6 to 8 years

Conclusions

The results of these trials indicate that betamethasone dipropionate is capable of producing the signs and symptoms of corticosteroid related toxicity from any of the four formulations. As a surrogate of in vivo bioavailability the detection of systemic side effects (ie., HPA axis suppression) indicates that pharmacologically significant amounts of corticosteroid are being absorbed.

Recommendations

Based on the wide range of corticosteroid toxicity seen in these patients, across all products and ranges of age, the use of these agents below the age of 12 is not recommended. This recommendation has been forwarded to the reviewing Medical Officer (Dr. Denise Cook) and appropriate labeling will be developed to convey the risk of corticosteroid related adverse events.

Dennis Bashaw, Pharm.D.
Team Leader, HFD-540/550/560
PK Review Team

Secondary Review: Arzu Selen, Ph.D., Deputy Director, DPE-III_____

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Detailed Study Synopsis

Title of Study: Phase IV Multicenter, Open-Label Safety Studies (Four Protocols Combined) in Pediatric Patients with Atopic Dermatitis, Treated with Betamethasone Dipropionate (SCH-11460) 0.05% Formulations (Diprolene AF Cream, Diprosone Ointment, Diprosone Cream, and Diprosone Lotion) Twice Daily (Protocols P01260, P01261, P01262. P01263).

Investigator(s): Multicenter: P01 260 (Diprolene AF Cream) - 7 centers
P01 261 (Diprosone Ointment) - 8 centers
P01 262 (Diprosone Cream) - 8 centers
P01 263 (Diprosone Lotion) - 5 centers

Studied Period: P01 260 - 25 January 2000 to 5 September 2000
P01 261 - 21 January 2000 to 20 October 2000
P01 262 - 17 January 2000 to 7 September 2000
P01 263 - 7 January 2000 to 13 May 2000

Objective(s): To determine the local and systemic safety of betamethasone dipropionate 0.05% formulations (Diprolene AF cream, Diprosone ointment, Diprosone cream, and Diprosone lotion) when used for the treatment of corticosteroid-responsive dermatoses (atopic dermatitis) in pediatric patients aged 3 months to 12 years.

Methodology: Multicenter, open-label, safety studies 2 to 3 week treatment with 2 to 4 week follow-up.

Diagnosis and Criteria for Inclusion:

- Patients 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, overall disease severity must have been moderate to severe, and total sign/symptom score must have been at least 9.

- Patients must have had disease involving 35% or greater of the body surface area.

- Patients must have demonstrated normal or clinically acceptable morning serum cortisol levels and normal HPA (hypothalamic-pituitary-adrenal) axis 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.

- Patients must not have required any other medication (topical or systemic) that may have affected the HPA axis or topical safety, or the course of the disease during the study period.

- Patients must not have taken immunosuppressive medication (including systemic steroids) within one month prior to Study Day 1 (day of Baseline evaluations and first day of treatment), and must not have used topical corticosteroids within 7 days prior to enrollment or systemic corticosteroids 28 days prior to enrollment.

- Patients must have been free of chronic diseases (eg, diabetes, renal, hepatic) which could have interfered with interpretation of study results.

- Patients must not have exhibited clinical signs of pre-existing skin atrophy in, or nearby, treatment areas; and must have been free of suspected cutaneous infection of the skin.

Test Product:
The following study medications were applied topically on selected skin areas twice a day for two to three weeks:

Product	Strength	Batch #	Protocol #
Diprolene AF Cream	0.05%	[redacted]	(ProtocolPO1260)
Diprosone Ointment	0.05%		(ProtocolPO1261)
Diprosone Cream	0.05%		(ProtocolPO1262)
Diprosone lotion	0.05%		(Protocol P01263)

Criteria for Evaluation:
The primary safety endpoints of these studies were the changes in serum cortisol levels in response to Cortrosyn® (cosyntropin) stimulation (HPA axis function), and clinical signs of cutaneous atrophy. HPA axis function was evaluated by assessing levels of serum cortisol prior to and 30 minutes after Cortrosyn® challenge at Baseline (Visit 1, Day 1) and at End of Treatment (Visit 3, Day 15, or Visit 4, Day 22).

Statistical Methods:
Statistical methods include summary/descriptive statistics of baseline and demographic variables, as well as listings and summaries of adverse events, skin atrophy, serum cortisol levels, response to Cortrosyn® testing, and routine laboratory values.

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Table I

Timepoint Cortisol Level	[illegible] mo - [illegible] yr (n=2)	[illegible] yr - 5 yr (n=15)	6 yr - 8 yr (n=25)	9 yr - 12 yr (n=12)	Total (n=54)
	Age Group				
Baseline					
n	2	15	25	12	54
Pre-Cortrosyn®					
<=5 µg/dL	0 (0)	1 (7)	1 (4)	1 (8)	3 (6)
>5 µg/dL	2 (100)	14 (93)	2[illegible] (96)	11 (92)	51 (94)
Post-Cortrosyn®					
<=18 µg/dL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
>18 µg/dL	2 (100)	15 (100)	25 (100)	12 (100)	54 (100)
Pre/Post Difference					
<7 µg/dL	0 (0)	0 (0)	[illegible] (4)	1 (8)	2 (4)
>=7 µg/dL	2 (100)	15 (100)	2[illegible] (96)	11 (92)	52 (96)
Endpoint					
n	2	15	25	12	54
Pre-Cortrosyn®					
<=5 µg/dL	0 (0)	2 (13)	1 (4)	1 (8)	4 (7)
>5 µg/dL	2 (100)	13 (87)	24 (96)	11 (92)	50 (93)
Post-Cortrosyn®					
<=18 µg/dL	0 (0)	5 (33)	4 (16)	1 (8)	10 (19)
>18 µg/dL	2 (100)	10 (67)	21 (84)	11 (92)	44 (81)
Pre/Post Difference					
<7 µg/dL	1 (50)	2 (13)	5 (20)	1 (8)	9 (17)
>=7 µg/dL	1 (50)	13 (87)	20 (80)	11 (92)	45 (83)
Per Cortrosyn® Labeling HPA Axis Suppression at Endpoint a	1 (50)	6 (40)	8 (32)	2 (17)	17 (31)
2 Week Follow up					
n	0	2	2	0	4
Pre-Cortrosyn®					
<=5 µg/dL		0 (0)	0 (0)		0 (0)
>5 µg/dL		2 (100)	2 (100)		4 (100)
Post-Cortrosyn®					
<=18 µg/dL		0 (0)	0 (0)		0 (0)
>18 µg/dL		2 (100)	2 (100)		4 (100)
Pre/Post Difference					
<7 µg/dL		0 (0)	0 (0)		0 (0)
>=7 µg/dL		2 (100)	2 (100)		4 (100)

* Data not available or data not applicable.
a: Total number of subjects with a per Cortrosyn®* HPA axis suppression - with a pre Cortrosyn®* stimulation value <=5 µg/dL or a post Cortrosyn®* cortisol value <=18 µg/dL or a pre/post Cortrosyn®* difference of <[illegible] µg/dL.
Note: 2 week follow up test was done only if end of treatment test (Day 15 or 22) was abnormal.
Endpoint = end of treatment.

Table II

[illegible] Research Institute
Phase IV Multi-Center, Open Label Study in
Pediatric Subjects with Atopic Dermatitis

Tacrolimus Ointment: Distribution Number (%) of Subjects Based on Response to Cortrosyn® Stimulation at Baseline and at Endpoint, By Category (Subjects with Pre- and Post Cortrosyn® Cortisol Values) (N=64)
[illegible]

Timepoint* Cortisol Level	Age Group: [illegible] - 1 yr (n=11)	2 yr - 5 yr (n=22)	6 yr - 8 yr (n=21)	9 yr - 12 yr (n=10)	Total (n=64)
Baseline					
n	11	22	21	10	64
Pre Cortrosyn®					
<5 µg/dL	0 (0)	0 (0)	3 (14)	2 (20)	5 (8)
>=5 µg/dL	11 (100)	22 (100)	18 (86)	8 (80)	59 (92)
Post Cortrosyn®					
<=18 µg/dL	0 (0)	1 (5)	4 (19)	2 (20)	7 (11)
>18 µg/dL	11 (100)	21 (95)	17 (81)	8 (80)	57 (89)
Pre/Post Difference					
<7 µg/dL	1 (9)	2 (9)	4 (19)	1 (10)	8 (13)
>=7 µg/dL	10 (91)	20 (91)	17 (81)	9 (90)	56 (88)
Endpoint					
n	11	22	21	10	64
Pre Cortrosyn®					
<5 µg/dL	1 (9)	1 (5)	1 (5)	1 (10)	4 (6)
>=5 µg/dL	10 (91)	21 (95)	20 (95)	9 (90)	60 (94)
Post Cortrosyn®					
<=18 µg/dL	2 (18)	4 (18)	8 (38)	1 (10)	15 (23)
>18 µg/dL	9 (82)	18 (82)	13 (62)	9 (90)	49 (77)
Pre/Post Difference					
<7 µg/dL	2 (18)	6 (27)	6 (29)	1 (10)	15 (23)
>=7 µg/dL	9 (82)	16 (73)	15 (71)	9 (90)	49 (77)
Per Cortrosyn® Labeling HPA Axis Suppression at Endpoint^a	4 (36)	9 (41)	11 (52)	2 (20)	26 (41)
2-Week Follow up					
n	1	1	0	0	2
Pre Cortrosyn®					
<5 µg/dL	0 (0)	0 (0)			0 (0)
>=5 µg/dL	1 (100)	1 (100)			2 (100)
Post Cortrosyn®					
<=18 µg/dL	0 (0)	0 (0)			0 (0)
>18 µg/dL	1 (100)	1 (100)			2 (100)
Pre/Post Difference					
<7 µg/dL	0 (0)	0 (0)			0 (0)
>=7 µg/dL	1 (100)	1 (100)			2 (100)

* Data not available or data not applicable.
a: Total number of subjects with a per Cortrosyn®* HPA axis suppression: with a pre Cortrosyn®* stimulation value <5 µg/dL or a post Cortrosyn®* cortisol value <=18 µg/dL or a pre/post Cortrosyn®* difference of <7 µg/dL.
Note: 2-week follow up test was done only if end of treatment test (Day 15 or 22) was abnormal.
Endpoint = end of treatment.

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Table III

[illegible] Research Institute
Phase IV Multi-Center, Open Label Study in
Pediatric Subjects with Atopic Dermatitis

[illegible] Number (%) of Subjects [illegible] Response to Cortrosyn® Stimulation at Baseline and at
Endpoint, By Category Subjects with Pre- and Post Cortrosyn® Cortisol Values [illegible]
[illegible]

Age Group

Timepoint Cortisol Level	3 mo - 1 yr (n=3)	2 yr - 5 y (n=20)	6 yr - 8 yr (n=15)	9 yr - 12 yr (n=8)	Total (n=46)
Baseline					
n	3	20	15	7	45
Pre Cortrosyn®					
<5 μg/dL	0 (0)	1 (5)	0 (0)	1 (14)	2 (4)
≥5 μg/dL	3 (100)	19 (95)	15 (100)	6 (86)	43 (96)
Post Cortrosyn®					
<18 μg/dL	0 (0)	1 (5)	2 (13)	2 (29)	5 (11)
≥18 μg/dL	3 (100)	19 (95)	13 (87)	5 (71)	40 (89)
Pre/Post Difference					
<7 μg/dL	0 (0)	0 (0)	2 (13)	0 (0)	2 (4)
≥7 μg/dL	3 (100)	20 (100)	13 (87)	7 (100)	43 (96)
Endpoint					
n	3	20	15	8	46
Pre Cortrosyn®					
<5 μg/dL	0 (0)	4 (20)	1 (7)	1 (13)	6 (13)
≥5 μg/dL	3 (100)	16 (80)	14 (93)	7 (88)	40 (87)
Post Cortrosyn®					
<18 μg/dL	0 (0)	4 (20)	3 (20)	1 (13)	8 (17)
≥18 μg/dL	3 (100)	16 (80)	12 (80)	7 (88)	38 (83)
Pre/Post Difference					
<7 μg/dL	0 (0)	6 (30)	4 (27)	0 (0)	10 (22)
≥7 μg/dL	3 (100)	14 (70)	11 (73)	8 (100)	36 (78)
Per Cortrosyn® Labeling HPA Axis Suppression at Endpoint * a	0 (0)	7 (35)	6 (40)	1 (13)	14 (30)
2 Week Follow-up					
n	0	2	1	0	3
Pre Cortrosyn®					
<5 μg/dL		0 (0)	0 (0)		0 (0)
≥5 μg/dL		2 (100)	1 (100)		3 (100)
Post Cortrosyn®					
<18 μg/dL		1 (50)	0 (0)		1 (33)
≥18 μg/dL		1 (50)	1 (100)		2 (67)
Pre/Post Difference					
<7 μg/dL		2 (100)	0 (0)		2 (67)
≥7 μg/dL		0 (0)	1 (100)		1 (33)

* Data not available or data not applicable.
a: Total number of subjects with a per Cortrosyn® HPA axis suppression: with a pre Cortrosyn® stimulation value <5 μg/dL or a post Cortrosyn® cortisol value <18 μg/dL or a pre/post Cortrosyn® difference of <7 μg/dL.
Note: 2 week follow up test was done only if end of treatment test (Day 15 or 22) was abnormal.
Endpoint = end of treatment.

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Table IV

Schering-Plough Research Institute
Phase IV Multi-Center, Open Label Study in
Pediatric Subjects with Atopic Dermatitis

Diprolene Lotion: Distribution (Number [%]) of Subjects Based on Response to Cortrosyn® Stimulation at Baseline and at Endpoint, By Category (Subjects with Pre and Post Cortrosyn® Cortisol Values) (N=16)
(HPTT)

Timepoint Cortisol Level	Age Group: 3 mo - 2 yr (n=0)	3 yr - 5 yr (n=0)	6 yr - 8 yr (n=11)	9 yr - 12 yr (n=5)	Total (n=16)
Baseline					
n			11	5	16
Pre-Cortrosyn®					
<5 µg/dL			3 (27)	0 (0)	3 (19)
>=5 µg/dL			8 (73)	5 (100)	13 (81)
Post-Cortrosyn®					
<=18 µg/dL			3 (27)	0 (0)	3 (19)
>18 µg/dL			8 (73)	5 (100)	13 (81)
Pre/Post Difference					
<7 µg/dL			2 (18)	1 (20)	3 (19)
>=7 µg/dL			9 (82)	4 (80)	13 (81)
Endpoint					
n			11	5	16
Pre-Cortrosyn®					
<5 µg/dL			3 (27)	1 (20)	4 (25)
>=5 µg/dL			8 (73)	4 (80)	12 (75)
Post-Cortrosyn®					
<=18 µg/dL			7 (64)	4 (80)	11 (69)
>18 µg/dL			4 (36)	1 (20)	5 (31)
Pre/Post Difference					
<7 µg/dL			5 (45)	4 (80)	9 (56)
>=7 µg/dL			6 (55)	1 (20)	7 (44)
Per Cortrosyn® Labeling HPA Axis Suppression at Endpoint a			8 (73)	4 (80)	12 (75)
2-Week Follow-up					
n			5	2	7
Pre-Cortrosyn®					
<5 µg/dL			0 (0)	0 (0)	0 (0)
>=5 µg/dL			5 (100)	2 (100)	7 (100)
Post-Cortrosyn®					
<=18 µg/dL			1 (20)	0 (0)	1 (14)
>18 µg/dL			4 (80)	2 (100)	6 (86)
Pre/Post Difference					
<7 µg/dL			[illegible] (80)	1 (50)	[illegible]
>=7 µg/dL			1 (20)	1 (50)	[illegible]

'-' Data not available or data not applicable.
a: Total number of subjects with a per Cortrosyn®* HPA axis suppression: with a pre Cortrosyn®* stimulation value <5 µg/dL or a post Cortrosyn®* cortisol value <= 18 µg/dL or a pre/post Cortrosyn®* difference of <7 µg/dL.
Note: 2-week follow up test was done only if end-of treatment test (Day 15 or 22) was abnormal.
Endpoint = end of treatment.