CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-844

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

PRODUCT (Generic Name):	Desonide (0.05%) Gel
PRODUCT (Proposed Brand Name):	Desonate™ HydroGel™
DOSAGE FORM:	Topical Gel
NDA:	21- 844
SUBMISSION DATE:	December 19, 2005
SPONSOR:	Dow Pharmaceutical Sciences
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Edward D. Bashaw, Pharm. D.
OCPB DIVISION:	DPE III, HFD 880
OND DIVISION:	HFD 540

Desonide (0.05%) Topical Gel (NDA 21-844) Clinical Pharmacology Review Addendum

In the pre-NDA meeting held on February 10, 2005, the sponsor was requested to address "the systemic exposure of desonide and its metabolite following application of the final market formulation of Desonide Gel, 0.05% under maximal usage condition in the target patient population." The sponsor subsequently submitted NDA 21-844 for this drug product on December 19, 2005, without addressing this issue. It is noted, however, that in the pre-IND meeting held on October 3, 2001, the sponsor was advised that "in lieu of" in vivo biostudies using plasma levels, both the HPA axis suppression and the topical vasoconstrictor studies would be required. As is evident from the NDA submission, the sponsor did conduct both vasoconstrictor and HPA-axis suppression studies in this application as surrogate measures of systemic exposure, As the sponsor has followed all of the current Agency guidances for assessing the in vivo bioavailabilty of topical corticosteroid drug products, no further information will be necessary for this application. The request for an in vivo assessment of systemic exposure contained in the pre-NDA meeting can be waived for this application. However, as standards evolve future applications may require an assessment of in vivo systemic exposure for filing.

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/s/

Tapash Ghosh
9/21/2006 03:41:19 PM
BIOPHARMACEUTICS

Dennis Bashaw
9/22/2006 12:27:54 PM
BIOPHARMACEUTICS

Clinical Pharmacology Review

PRODUCT (Generic Name):	Desonide (0.05%) Gel
PRODUCT (Proposed Brand Name):	Desonate™ HydroGel™
DOSAGE FORM:	Topical Gel
NDA:	21- 844
PROPOSED INDICATIONS:	Atopic Dermatitis
NDA TYPE:	505 (b) (2)
SUBMISSION DATE:	December 19, 2005
SPONSOR:	Dow Pharmaceutical Sciences
REVIEWER:	Tapash K. Ghosh, Ph.D.
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EXECUTIVE SUMMARY

Desonide Gel, 0.05%, is a new topical drug formulation of desonide that is under review for the treatment of atopic dermatitis. Desonide is considered a low-potency corticosteroid and is currently approved in the U.S. in three different dosage forms for topical use: cream, ointment, lotion, all at a strength of 0.05%. In addition to the initial product line (Tridesilon®), several commercial and generic dosage forms are available.

The Dow Pharmaceutical Sciences clinical development program for Desonide Gel consisted of five studies that included the standard set of studies for evaluation of topical corticosteroid therapies. The clinical pharmacology studies included a hypothalamic-pituitary- adrenal (HPA) axis suppression study in subjects with atopic dermatitis and one vasoconstriction studies in healthy volunteers to evaluate the potency of the proposed Desonide Gel 0.05%.

The data demonstrate that the vasoconstrictive properties of Desonide Gel are comparable to DesOwen® Lotion, a group VI corticosteroid. In the HPA axis trial, all 34 subjects (100%) in the modified intent-to-treat population showed normal adrenal

response following 4 weeks of twice daily applications of study medication. There were no unexpected safety findings for Desonide Gel, 0.05%.

Recommendation:

The Clinical Pharmacology and Biopharmaceutics section of NDA 21 - 844 is acceptable with no suggestion for labeling changes.

Primary Reviewer: Tapash K. Ghosh, Ph.D.
Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation III

Team Leader: Edward D. Bashaw, Pharm.D._____

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Background: The proposed product in this 505(b) (2) application, Desonide Gel 0.05%, has been developed for the topical treatment of atopic dermatitis in pediatric patients. The gel formulation offers a unique dosage form that may offer cosmetic advantages over ointments and creams in that it is less greasy and is easier to apply.

Due to their anti-inflammatory, antipruritic, and vasoconstrictive actions, topical corticosteroids, including desonide, are often used for the treatment of corticosteroid-responsive dermatoses of the skin and scalp, including contact dermatitis, atopic dermatitis, and seborrheic dermatitis. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Desonide Gel 0.05%, is a topical gel used for treatment of mild to moderate atopic dermatitis. The gel is essentially

The clinical development program for Desonide Gel consisted of five studies that included the standard set of studies for evaluation of topical corticosteroid therapies. There were two clinical pharmacology studies. The first one was A Single-point, Randomized, Evaluator Blinded, Within Subject, Single Center Evaluation of the Vasoconstrictive Properties of Desonide Gel 0.05% in Normal Healthy Volunteers (Study No. 7001-G3HP-02-03). This masked (evaluator and subject) study was designed to compare the vasoconstriction effect of a new gel based Desonide formulation to three other commercially available topical corticosteroid formulations: DesOwen® Lotion (desonide lotion 0.05%), hydrocortisone cream 0.5% (low potency), and Cyclocort® Cream (amcinonide 0.1%, high potency) in 36 (6M; 30F; 27 Caucasian; 3 Hispanic; 6 Asian) healthy volunteers. Potency was assessed using the vasoconstriction response of the skin following a16 hour dose exposure duration to each formulation as measured using the chromometer. Overall, the data demonstrate that the vasoconstrictive properties of Desonide Gel are comparable to DesOwen® Lotion, a group VI corticosteroid.

The second study was A Multi-Center, Open-Label Evaluation of the Adrenal Suppression Potential of Topically Applied Desonide Gel 0.05% in Pediatric Subjects with Moderate to Severe Atopic Dermatitis (Study No. 7001-G3HP-03-03) in 40 evaluable pediatric subjects with moderate to severe atopic dermatitis with a minimum of 35% body surface area (BSA). A baseline Physician's Global Severity Score and baseline erythema score rated as moderate or severe and a normal serum cortisol response was required at screening for enrollment. In this trial, all 34 subjects (100%) in the modified (as defined in individual study report **Study 7001-G3HP-03-03)** intent-to-treat population showed normal adrenal response with no unexpected safety findings following 4 weeks of twice daily applications of study medication. The study medication was

tolerated by the pediatric subjects enrolled into this clinical study, age 3 months to 5 years 11 months. Inter-individual fluctuations in pre- and post-stimulation plasma cortisol levels over the 4-week treatment were determined by the study endocrinologist to be normal physiological variations.

The following text on efficacy and safety have been excerpted from the sponsor's document.

"The efficacy of Desonate HydroGel, 0.05% in atopic dermatitis has been demonstrated in two adequate and well-controlled clinical studies. The first Phase 3 study (7001-G3HP-04-03) was a randomized, evaluator-blind, 3-arm, multi-center study, and the other (7001-G3HP-01-05) was a randomized, double-blind, placebo-controlled, multicenter study, to assess the safety and efficacy of Desonide Gel 0.05% in pediatric patients with mild to moderate atopic dermatitis. Application of the study medication was made by the subject to affected lesions twice daily for 4 weeks. Patients ranging in age between 3 months to 18 years were treated twice daily for 4 weeks with either Desonate Hydrogel, 0.05% or vehicle HydroGel. Efficacy assessments were based on investigator assessments of the signs and symptoms of atopic dermatitis. The primary measure of efficacy was the Investigator's Global Severity Score (IGSS) at Week 4 comparing treatment success of Desonate HydroGel, 0.05% with that of the HydroGel vehicle. Treatment success was defined as a 2 point change (decrease) from the subject's baseline IGSS when compared to the Week 4 IGSS. For example, if a subject's baseline IGSS was 2 (mild) at baseline, and decreased to 0 (clear) at Week 4, this was considered a treatment success. The results of the 2 clinical trials are summarized in the following table:

Primary Efficacy Percent Success Rate*	**Clinical Trial 1**		**Clinical Trial 2**	
	Desonate HydroGel (N = 289)	HydroGel Vehicle (N = 92)	Desonate HydroGel (N = 136)	HydroGel Vehicle (N = 65)
	128 (44%)	**13 (14%)**	**38 (27.9%)**	**4 (6.2%)**

*At 4 weeks study duration

In another study the effects of Desonate HydroGel, 0.05% on hypothalamic-pituitary-adrenal (HPA) axis suppression were studied in patients of age 3 months to 5 years, 11 months. A Physician's Global Severity Score was used for the assessment of efficacy during this 4 week study. The success rate at 4 weeks was 55% in this group of 40 patients.

The Clinical Safety Evaluation includes studies of cumulative irritation (n = 227), contact sensitization repeat insult patch test (n = 230), vasoconstrictive potential (n = 36), HPA suppression (n = 40), and two safety and efficacy studies in pediatric patients with mild-to-moderate atopic dermatitis (n = 425). No significant evidence of irritation, sensitization, HPA axis suppression or other local or systemic side effects were found in these studies."

GENERAL ATTRIBUTES

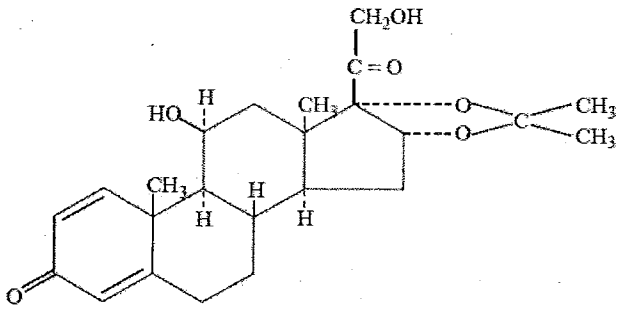
Trade name: Desonate™ ——— ™ (Desonide Gel 0.05%

Generic name: Desonide

Chemical name: (11β, 16α)-11,21-dihydroxy-16,17-[(1- methylethylidene)bis(oxy)]-pregna-1,4-diene-3,20-dione

Molecular formula/molecular weight: $C_{24}H_{32}O_6$/416.51

Chemical Structure:



Description and Composition of the Drug Product:

Desonide Gel 0.05%, is a topical gel used for treatment of mild to moderate atopic dermatitis. The gel is essentially ——— It contains desonide, ——— Desonide, ——— Desonide Gel 0.05% will be filled and packaged in 3 commercial package sizes (i.e. 15-g, 30-g and 60-g ——— tubes) and a physician sample container (i.e. 3.5-g tube). A complete description of the quantitative composition of the finished product is provided in the following Table.

5 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

INDIVIDUAL STUDY REVIEWS:

NDA: 21-844/Study 7001-G3HP-02-03 **Study Dates: Sep, 03 – Oct, 03**

A Single-point, Randomized, Evaluator Blinded, Within Subject, Single Center Evaluation of the Vasoconstrictive Properties of Desonide Gel 0.05% in Normal Healthy Volunteers

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Objective of the Study: The primary objective of the study was to demonstrate the relative vasoconstrictive potential of Desonide Gel 0.05% compared to the gel vehicle, DesOwen® Lotion (desonide lotion 0.05%), hydrocortisone cream 0.5% (low potency), and Cyclocort® Cream (amcinonide 0.1%, Fujisawa Healthcare Inc.).

Study Design: This single center, masked (evaluator and subject) study was designed to compare the vasoconstriction effect of a new gel based Desonide formulation to three other commercially available topical corticosteroid formulations: DesOwen® Lotion (desonide lotion 0.05%), hydrocortisone cream 0.5% (low potency), and Cyclocort® Cream (amcinonide 0.1%, Fujisawa Healthcare Inc.) in 36 (6M; 30F; 27 Caucasian; 3 Hispanic; 6 Asian) healthy volunteers. The primary efficacy measurement was a visual assessment of vasoconstriction (i.e. skin blanching); the secondary efficacy measurement was a chromametric assessment of vasoconstriction.

On Day 1 of the study, three 1cm^2 test sites were identified on the right ventral forearm and four such sites on the left ventral forearm. Sites were marked with an indelible pen. Baseline chromametric readings were taken from these sites using a [redacted]. Approximately ten (10) milligrams of each study medication were applied to each of the designated test sites using a fresh cotton-tipped applicator for each site. All of the treatments were applied later in the afternoon (e.g., at approximately 4:00 PM) on Day 1, after which the test sites were protected using a raised perforated guard secured to the arm with a nonocclusive tape. The next day, per instructions from the research center staff, while at home and 16 hours (±1 hour) after the study medication applications, the subjects removed the protective guards and gently washed the test sites with mild soap and water. Upon return to the clinic two hours later (18 hours ± 1 hour after the study medication applications; e.g., 10:00 AM based upon a 4:00 PM application time on Day 1), an experienced evaluator performed the visual assessment of vasoconstriction (skin-blanching) based on a four-point scale (0-3).

Changes in chromametric values were calculated as follows: the values for each subject's Day 1 (baseline) measurements were subtracted from their respective Day 2 (postapplication) values to determine the change in skin blanching at each test site (change in chromametric measurement). This delta value obtained for each subject from his or her chromametric control site was used as a correction factor. This correction factor was then subtracted from the change in chromametric measurement at each test site

(corrected change in chromametric measurement). The mean values (from the analysis of variance) for each of these corrected changes in chromametric measurement parameters for each study medication were compared using the [redacted]. The primary efficacy measurement was a visual assessment of vasoconstriction; the secondary efficacy measurement was a chromametric assessment of vasoconstriction. Subject safety was evaluated through adverse event reporting.

Efficacy Results and Tabulations of Individual Patient Data Analysis of Efficacy

Visual Assessments: The mean scores for visual vasoconstriction assessment are shown in Figure 1 below. Cyclocort® Cream was statistically more vasoconstrictive than all other study medications. The desonide-containing study medications were intermediate in vasoconstrictive effect and not statistically different from one another. The 0.5% hydrocortisone cream and the Desonide GelVehicle were significantly the least vasoconstrictive of the study medications and were not statistically different from one another.

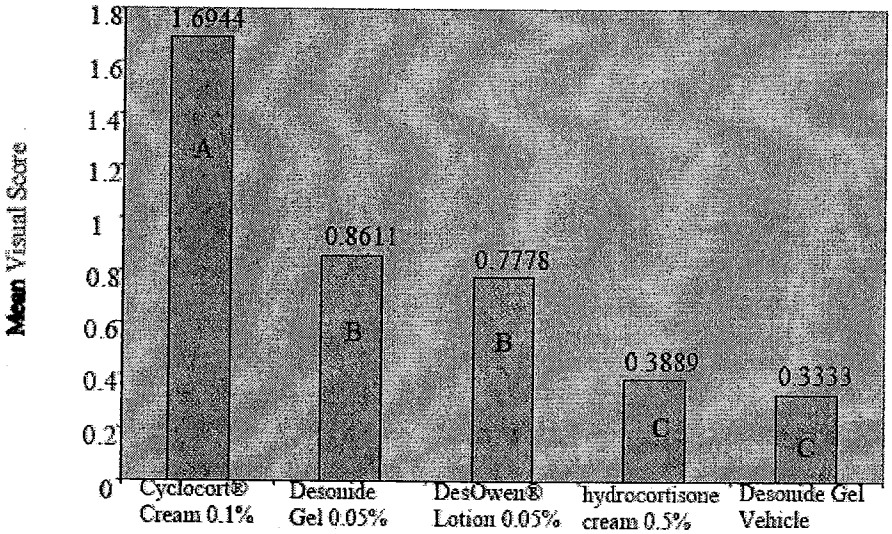

Figure 1: Visual Assessment Scores – Study drugs separated into three groups based upon statistical analysis – Cyclocort® Cream alone in group A, desonide-containing products in group B, 0.5% hydrocortisone and Desonide Gel Vehicle in group C.

Chromametric Assessments: The average corrected values for the chromametric red-green (a) values are shown in Figure 2 below. Cyclocort® Cream 0.1% and the desonide-containing study medications were not statistically different from each other and are grouped together in the greater vasoconstrictive group. The 0.5% hydrocortisone cream and the Desonide Gel Vehicle were significantly less vasoconstrictive than the foregoing (and made up the lesser vasoconstrictive group) and were not statistically different from one another.

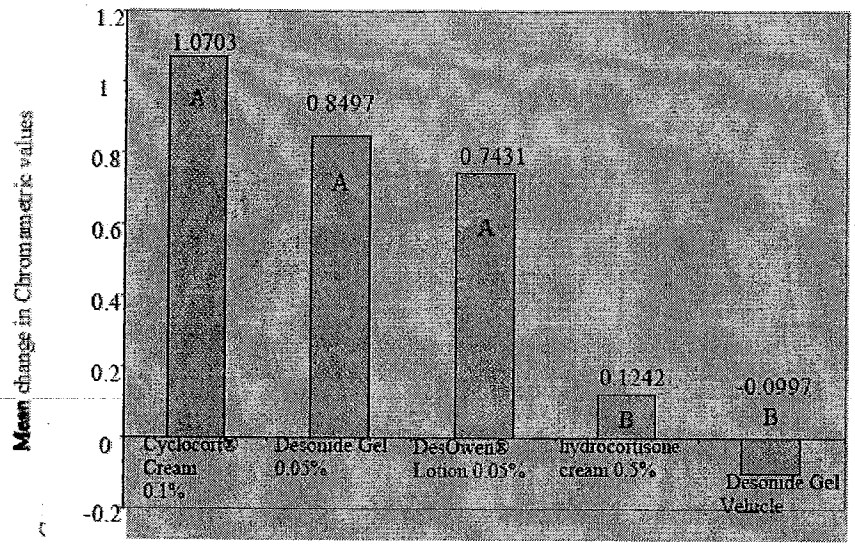

Figure 2: Corrected change in 'a' values (red-green) - Study medications separated into two groups based upon statistical analysis – Cyclocort® Cream and the desonide-containing products in group A, 0.5% hydrocortisone and Desonide Gel Vehicle in group B.

Discussion and overall Conclusions: *Visual Assessment of Vasoconstriction:* Using this method, the Desonide Gel 0.05% investigational medication was not statistically different from DesOwen® Lotion. These were bracketed by the selected statistically significant higher and lower vasoconstrictive potency study medications, Cyclocort® Cream 0.1% and hydrocortisone cream 0.5% respectively. These results, demonstrate a vasoconstriction potency ranking for Desonide Gel 0.05% equivalent to that of DesOwen® Lotion 0.05% (group VI).

Chromametric Measurement of Vasoconstriction: In this study, as a secondary efficacy endpoint, the chromametric measurement supports the findings of the visual assessment. The ordinal ranking of each study medication in the chromametric analysis was identical to that in the visual analysis. Statistically, the desonide-containing study medications did not separate from one another or from the Cyclocort® Cream 0.1%, but all were found to be statistically more vasoconstrictive than hydrocortisone cream 0.5% or the Desonide Gel Vehicle. This difference in result from the visual approach may be due to the fact that the potency ranking of the reference products used in this study were established using a visual scoring method which is felt by the dermatologic community to better reflect clinical practice.

Overall. the data demonstrate that the vasoconstrictive properties of Desonide Gel are comparable to DesOwen® Lotion, a group VI corticosteroid. There appear to be no significant safety findings associated with the investigational product.

Comment: *Potency was assessed using the vasoconstriction response of the skin following a 16 hour dose exposure duration to each formulation as measured using the chromameter. As the sponsor did not conduct any pilot study to ascertain this dose duration and relied on the literature value for that purpose, they should have mentioned that clearly in their report.*

NDA: 21-844/Study 7001-G3HP-03-03 **Study Dates: Mar, 04 –Sep, 04**

A Multi-Center, Open-Label Evaluation of the Adrenal Suppression Potential of Topically Applied Desonide Gel 0.05% in Pediatric Subjects with Moderate to Severe Atopic Dermatitis

Objectives:

The objective of this study was to determine the safety and systemic tolerance of Desonide Gel 0.05% in the treatment of pediatric subjects with moderate to severe Atopic Dermatitis (AD).

Methodology:

This was a multicenter (5 centers), open-label study in 40 evaluable pediatric subjects with moderate to severe atopic dermatitis to assess the safety of Desonide Gel including its effect on the HPA axis, as measured by cosyntropin stimulated changes in serum cortisol response. Subjects who met all inclusion and exclusion criteria including having AD that involved a minimum of 35% body surface area (BSA), a baseline Physician's Global Severity Score and baseline erythema score rated as moderate or severe and a normal serum cortisol response at screening were eligible to enter the study. The Subject's parent or guardian was instructed to apply the study medication to all affected areas 2 times daily (morning and evening) in a thin film rubbed gently into skin daily for 4 weeks. The Investigator recorded the percentage of body surface area affected by atopic dermatitis for each of the 5 areas (Face, scalp, arms, trunk and legs) of the body. The total BSA was computed as the sum of the percentage BSA reported for the 5 body regions. The Investigator also recorded the percentage of body surface area being treated with study drug at Baseline and Week 2.

Blood samples were obtained and the adrenal function test was performed using the cosyntropin stimulation test (CST) at Baseline/Day 1 and at Week 4, Day 28 as follows:

- Prior to 8:30 a.m., a blood sample (pre-stimulation) was obtained for plasma cortisol level.
- Immediately following the pre-stimulation blood sample, reconstituted cosyntropin was administered intravenously using the 0.25 mg dose for the older cohort of children, and the 0.125mg dose for the younger cohort of children. The cosyntropin injection was administered over a two minute period as defined in the Cortrosyn® manufacturer's instructions.
- 30 minutes post cosyntropin administration, a blood sample (post-stimulation) was obtained.

If abnormal plasma cortisol levels were obtained on Day 1, the subject was discontinued from the study immediately and referred to their private physician for follow up. If

abnormal plasma cortisol levels were obtained at the Week 4/Day 28 visit, additional blood samples were required.

Plasma cortisol testing was performed via High Performance Liquid Chromatography with detection by [redacted] Spectrometry, using a [redacted] standard. The testing was done by [redacted]

A primary efficacy determination was based on the Investigator's evaluation of the signs and symptoms of AD (Erythema, Induration, and Oozing/Crusting) scored and recorded for each of the 5 sections of the body (face, scalp, arms, trunk, and legs).

Adverse Events Evaluations of skin atrophy, thin, shiny skin, striae, secondary infection, burning/stinging, dryness, scaling, telangiectasia, hypertrichosis, miliaria, ecchymoses, and sensitization were performed at each visit.

Disposition of Subjects:

Number of Subjects Planned: 40 subjects, 15 evaluable subjects per age cohort
Number of Subjects Enrolled: 40 subjects
Cohort 1: 3 months to 2 years 11 months; enrolled 20 subjects
Cohort 2: ≥ 3 years to 5 years 11 months; enrolled 20 subjects
Gender: Male: 17 Female: 23
Ethnicity (Race): Caucasian: 15 , Black: 13, Hispanic: 6, Asian: 5, Other: 1

All 40 subjects enrolled were included in the intent-to-treat (ITT) analyses. A total of 6 subjects were excluded from the modified intent-to-treat (MITT) population, 5 subjects in the 3 months to 2 years 11 months cohort and 1 subject in the 3 years to 5 years 11 months cohort as described in the following Tables.

Table 1: Protocol Deviations that Disqualified Subjects from the Modified Intent-to-Treat Population

	3 Mths to 2 Yrs 11 Mths	3 Yrs to 5 Yrs 11 Mths	All Subjects
Number of Subjects	20	20	40
Number of Subjects with Deviations	5	1	6
Deviation[a]			
Abnormal Baseline Plasma Cortisol Level	2	0	2
Missing Baseline Post-Stimulation Cortisol Level	1	0	1
Baseline Post-Stimulation Time >55 Minutes from Time of Cosyntropin Injection	1	0	1
Week 4 Post-Stimulation Time >55 Minutes from Time of Cosyntropin Injection	1	1	2

Table 2: Efficacy and Safety Measurements Assessed and Flow Chart

EFFICACY AND SAFETY EVALUATIONS			
Parameter	**Visit 1 Baseline/Day 1**	**Visit 2 Week2/Day 14**	**Visit 3 Week 4/Day 28**
Evaluation Variables			
Adrenal Function Test	X		X
Physician's Global Severity Score	X	X	X
Signs and Symptoms of AD	X	X	X
% BSA affected by AD	X	X	X
Safety Variables			
Adverse Events		X	X
Skin Irritation Evaluation	X	X	X

Results: Table 3 summarizes the cortisol levels at baseline and at the end of treatment, Week 4 visit for the modified intent-to-treat population by age cohort. The criterion to establish a normal response is a post-injection serum cortisol level greater than 18 mcg/dL.

Table 3: Summary of Cortisol Levels (µg/dL) at Baseline and End of Treatment (Week 4) (Modified Intent-to-Treat Subjects)

	3 Months to 2 Years 11 Months			3 Years to 5 Years 11 Months		
Baseline Cortisol Levels	Pre-Stimulation	Post-Stimulation	Change from Pre to Post[a]	Pre-Stimulation	Post-Stimulation	Change from Pre to Post[a]
N	15	15	15	19	19	19
Mean	13.71	25.87	12.16	9.68	25.21	15.53
STD	8.43	6.94	4.53	2.58	4.13	4.09
Week 4 Cortisol Levels	Pre-Stimulation	Post-Stimulation	Change from Pre to Post[a]	Pre-Stimulation	Post-Stimulation	Change from Pre to Post[a]
N	15	15	15	19	19	19
Mean	12.26	24.53	12.27	9.94	25.01	15.07
STD	4.26	3.78	4.16	3.34	3.73	3.45

	Week 4 Change from Baseline[b]		Week 4 Change from Baseline[b]	
Cortisol Levels	Pre-Stimulation	Post-Stimulation	Pre-Stimulation	Post-Stimulation
N	15	15	19	19
Mean	-1.45	-1.33	0.26	-0.21
STD	7.83	4.82	2.74	3.95

	All MITT Subjects		
Baseline Cortisol Levels	Pre-Stimulation	Post-Stimulation	Change from Pre to Post[a]
N	34	34	34
Mean	11.46	25.50	14.04
STD	6.16	5.46	4.55
Week 4 Cortisol Levels	Pre-Stimulation	Post-Stimulation	Change from Pre to Post[a]
N	34	34	34
Mean	10.96	24.80	13.84
STD	3.89	3.70	3.97

	Week 4 Change from Baseline[b]	
Cortisol Levels	Pre-Stimulation	Post-Stimulation
N	34	34
Mean	-0.49	-0.70
STD	5.55	4.32

[a] Change from pre-stimulation to post-stimulation was computed as post-stimulation minus pre-stimulation.
[b] Change from baseline was computed as Week 4 stimulation minus baseline.

Table 4: Incidence of Subjects with Normal and Suppressed Adrenal Function Results (Week 4) (Modified Intent-to-Treat Subjects)

	3 Mths to 2 Yrs 11 Mths (N=15)	3 Yrs to 5 Yrs 11 Mths (N=19)	All MITT Subjects (N=34)
Adrenal Function*	N %	N %	N %
Normal	15 (100%)	19 (100%)	34 (100%)
Suppressed	0 (0%)	0 (0%)	0 (0%)

* Adrenal suppression is defined as a post-stimulation cortisol peak value ≤ 18.0 µg/dL at Week 4.

All 34 subjects (100%) in the modified intent-to-treat population showed normal adrenal response following 4 weeks of twice daily applications of study medication.

The most common localized adverse events, dryness and scaling, were present at baseline and generally improved with treatment. Other reported adverse events were generally mild and not related to the study medication.

Efficacy results demonstrated an improvement in overall disease state, as measured by the Physician's Global Severity Scores, and individual signs of AD, including erythema, induration, oozing and crusting, and BSA affected. Improvement in the symptoms of AD was observed in both age cohorts and increased with continuing treatment from Week 2 to Week 4. In the intent-to-treat population, the treatment success rate at Week 2 was 45% (18/40 subjects) which increased to 55% (22/40 subjects) at Week 4. In the modified intent-to-treat population, the treatment success rate at Week 2 was 50% (17/34 subjects) and increased to 59% (20/34 subjects) at Week 4. Thus, the trial demonstrates the overall clinical benefit and satisfactory safety profile of Desonide Gel 0.05%

Conclusion: In this trial, all 34 subjects (100%) in the modified intent-to-treat population showed normal adrenal response following 4 weeks of twice daily applications of study medication. There were no unexpected safety findings for Desonide Gel, 0.05%. The study medication was tolerated by the pediatric subjects enrolled into this clinical study, age 3 months to 5 years 11 months. Inter-individual fluctuations in pre- and post-stimulation plasma cortisol levels over the 4-week treatment were determined by the study endocrinologist to be normal physiological variations.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-844**	**Brand Name**	Desonate™ HydroGel™
OCPB Division (I, II, III)	**III**	**Generic Name**	**Desonide**
Medical Division	**540**	**Drug Class**	**Corticosteroid**
OCPB Reviewer	**Tapash K. Ghosh**	**Indication(s)**	**Atopic Dermatitis**
OCPB Team Leader	**Dennis Bashaw**	**Dosage Form**	**Topical (0.05%) Gel**
		Dosing Regimen	**BID**
Date of Submission	**12/19/05**	**Route of Administration**	**Topical**
Estimated Due Date of OCPB Review	**07/19/06**	**Sponsor**	**Connectics**
PDUFA Due Date	**10/19/06**	**Priority Classification**	**1S**
Division Due Date			

Clin. Pharm. And Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
eers-				
single dose:				
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.

QBR questions (key issues to be considered)	**The potency ranking and the HPA axis suppression potential of the foam**
Other comments or information not included above	
Primary reviewer Signature and Date	**Tapash Ghosh 01-14-06**
Secondary reviewer Signature and Date	

CC: NDA 21-978, HFD-540 (Curtis), HFD-880(TL, DD, DDD),

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/s/

Tapash Ghosh
4/26/2006 10:30:16 AM
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Dennis Bashaw
4/27/2006 09:20:00 AM
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John P. Hunt
4/28/2006 03:44:13 PM
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