# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-978**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Clinical Pharmacology Review

| | |
|---|---|
| PRODUCT (Generic Name): | Desonide (0.05%) Foam |
| PRODUCT (Proposed Brand Name): | ——— Foam |
| DOSAGE FORM: | Topical Foam |
| NDA: | 21-978 |
| PROPOSED INDICATIONS: | Atopic Dermatitis |
| NDA TYPE: | 505(b) (1) |
| SUBMISSION DATE: | November 18, 2005 |
| SPONSOR: | Connectics |
| REVIEWER: | Tapash K. Ghosh, Ph.D. |
| TEAM LEADER: | Edward D. Bashaw, Pharm.D. |
| OCPB DIVISION: | DPE III, HFD 880 |
| OND DIVISION: | HFD 540 |

## EXECUTIVE SUMMARY

Desonide Foam, 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 Connetics clinical development program for Desonide Foam consisted of seven studies that included the standard set of studies for evaluation of topical corticosteroid therapies. As mutually agreed upon with the FDA, a direct assessment of *in vivo* bioavailability was not required for this product. The clinical pharmacology studies included a hypothalamic-pituitary- adrenal (HPA) axis suppression study in subjects with atopic dermatitis and two vasoconstriction studies (pilot and pivotal) in healthy volunteers to evaluate the potency of the proposed Desonide Foam 0.05%.

There was no significant difference in the vasoconstriction response between the Tridesilon Cream (0.05% Desonide) and the Desonide Foam 0.05% formulation. This

suggests that these two formulations should be considered within the same potency category (generally recognized as "mild" or "low" potency). The results of the safety analysis showed that the proportion of subjects determined to have demonstrated HPA axis suppression was 4% (3/75) of subjects overall. The most frequently reported AE was pyrexia. All treatment related AEs were mild to moderate application site reactions. There were no severe, serious or life-threatening adverse experiences or deaths reported during the study. None of the subjects in the study had serum glucose levels that were considered to be clinically significant.

A Phase 3 study evaluated the safety and efficacy of the proposed Desonide Foam 0.05% compared to its Vehicle Foam. As excerpted from the sponsor's version, the results of this study demonstrated that Desonide Foam was significantly more effective than placebo foam (for the primary and all of the secondary endpoints, $p < 0.0001$ for both the ITT and Per-Protocol populations) in reducing the manifestations of atopic dermatitis, as measured by treatment success. The mean percent reduction in the sum of the scores of erythema, induration/papulation, lichenification, scaling, and oozing/crusting from Baseline to Week 4 was 60.0% for ——— Foam vs. 20.9% for Vehicle Foam.

**Recommendation:**

The Clinical Pharmacology and Biopharmaceutics section of NDA 21-978 is acceptable with the suggested labeling changes as described below.

**CPB Labeling:** The following section should be added in the Pharmacokintics section of the labeling:

**Pharmacokinetics:**

*Treatment beyond 4 consecutive weeks is not recommended, because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. In a controlled pharmacokinetic study, 3 of 75 (4%) patients experienced ——— suppression of the adrenal following 4 weeks of ——— (desonide) Foam therapy.*

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Division of Pharmaceutical Evaluation III

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**Table of Contents**



## BACKGROUND

The proposed topical formulation Desonide Foam 0.05% (——— ™) submitted under section 505 (b) (1) is aimed to treat atopic dermatitis. 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.

The proposed Desonide Foam is a petrolatum-based emulsion aerosol foam containing the active ingredient desonide, a low-potency topical corticosteroid. It is dispensed from an aluminum can pressurized with a hydrocarbon (propane/butane) propellant. The foam delivery system has certain advantages over other currently marketed dosage forms. Cream and ointment dosage forms have aesthetic disadvantages in that these products may leave a greasy or sticky residue on the skin. Lotions may be runny, leading to loss of active ingredient at the desired site of action. In contrast, the foam is a non-runny vehicle. The foam is dispensed and massaged into the skin which collapses the foam structure, and deposits the active ingredient onto the skin. Better patient compliance may be expected with the foam formulation because of the localized application and improved aesthetic properties.

The Connetics clinical development program for Desonide Foam consisted of seven studies that included the standard set of studies for evaluation of topical corticosteroid therapies. Two studies were conducted in healthy volunteers to evaluate the potency of Desonide Foam: a vasoconstriction pilot study (DES.C.102) that was used to design the primary vasoconstriction study (DES.C.101), in which the potency of Desonide Foam was evaluated relative to other active corticosteroid therapies and to its Vehicle Foam. Two other studies in healthy volunteers evaluated: 1) the irritancy of Desonide Foam (DES.C.104) and 2) the ability of Desonide Foam to induce sensitization (DES.C.103). Because this drug is a corticosteroid, a hypothalamic-pituitary- adrenal (HPA) axis

suppression study (DES.C.201) was also completed in subjects with atopic dermatitis. A Phase 2 study (DES.C.202) was completed to evaluate the safety and efficacy of Desonide Foam compared to Vehicle Foam and to verify the sample size for the pivotal Phase 3 study, DES.C.301. The pivotal study was a single Phase 3 study (DES.C.301) designed to meet the criteria of being a very persuasive and highly robust study. This Phase 3 study evaluated the safety and efficacy of Desonide Foam compared to its Vehicle Foam.

As mutually agreed upon with the FDA, a direct assessment of *in vivo* bioavailability was not required for this product. A pilot vasoconstriction study (DES.C.102) was completed in healthy adult subjects. Potential subjects were screened for vasoconstriction responsiveness using two dose applications of Desonide Foam (one occluded and one non-occluded) on normal skin of the upper ventral arms (two sites). Eight dose durations ranging from 15 minutes to 6 hours were used to assess the topical vasoconstriction activity of Desonide Foam. Statistical evaluation of the $AUEC_{0-24h}$ dose-duration data from the occluded sites suggested an effective dose in 50% of the people ($ED_{50}$) of about 0.25 hours. Given the low vasoconstriction response observed at 0.25 hr, the Principal Investigator recommended that, for a pivotal potency ranking study, the $ED_{50}$ for Desonide Foam be tested at a dose duration no less than 0.25 hrs, and no greater than 1 hr, with the test sites occluded during the dose application period. In the primary vasoconstriction study (DES.C.101), thirty-six subjects were enrolled and treated with Desonide Foam, Elocon Cream, Tridesilon Cream and hydrocortisone cream to specific areas on the forearm. Potency was assessed by measuring the vasoconstriction response of the skin by chromameter following a 1 hour occluded dose exposure. Elocon (0.1% mometasone furoate) which is generally recognized as a moderate potency formulation, and thus by inference, would produce a greater vasoconstriction response over Desonide, did, in this study, demonstrate a lower AUEC, but statistically similar response to the Tridesilon Cream. This disparity in the Elocon response (verses its recognized potency ranking) is most likely attributable to the applied dose duration and occlusion of the applied dose. No measurable vasoconstriction response, above baseline, was observed for the Vehicle Foam, the non-treated control sites and for the hydrocortisone cream 0.5% formulation. There was no significant difference in the vasoconstriction response between the Tridesilon Cream (0.05% Desonide) and the Desonide Foam 0.05% formulation. This suggests that these two formulations should be considered within the same potency category (generally recognized as "mild" or "low" potency).

An HPA Axis suppression study (DES.C.201) assessed the effect of Desonide Foam on the HPA axis, as measured by the cosyntropin stimulated change in serum cortisol response. This was an open-label study that enrolled 81 subjects diagnosed with atopic dermatitis. Due to difficulty in obtaining blood samples pre- and post-stimulation at Week 4, there were a total of 75 evaluable subjects. All subjects had a minimum of 25% body surface area (BSA) involvement and a normal serum cortisol response at Screening. The criterion to establish a normal response was a post-injection serum cortisol level greater than 18 mcg/dL. The results of the safety analysis showed that the proportion of subjects determined to have demonstrated HPA axis suppression was 4% (3/75) of subjects overall.

A Phase 3, Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of Desonide Foam, 0.05%, in the Treatment of Adolescent and Pediatric Subjects with Mild to Moderate Atopic Dermatitis. The regulatory pathway chosen for this program was to conduct one very persuasive, highly robust, randomized, double-blind, vehicle-controlled Phase 3 study demonstrating the superiority of Desonide Foam to its vehicle. In this multicenter, randomized, double-blind, vehicle-controlled study of 581 patients with mild to moderate atopic dermatitis, Desonide Foam was applied twice daily for 4 weeks. Robustness was understood as: 1) a high level of statistical significance, 2) consistency of responses across sites, and 3) consistency of responses across subgroups (age cohort, gender, race, and disease severity). The results of this study demonstrated that Desonide Foam was significantly more effective than placebo foam (for the primary and all of the secondary endpoints, $p < 0.0001$ for both the ITT and Per-Protocol populations) in reducing the manifestations of atopic dermatitis, as measured by treatment success. The mean percent reduction in the sum of the scores of erythema, induration/papulation, lichenification, scaling, and oozing/crusting from Baseline to Week 4 was 60.0% for Desonide Foam vs. 20.9% for Vehicle Foam.

## GENERAL ATTRIBUTES

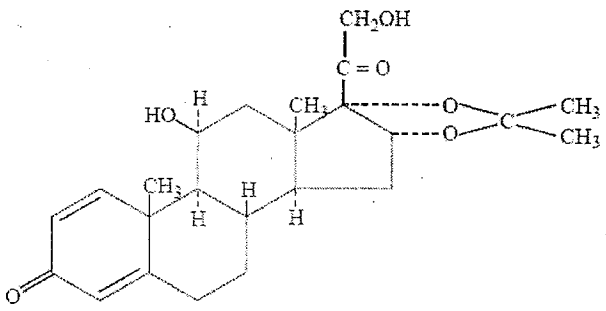
**Trade name:** ———™ (Desonide Foam 0.05%

**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 Foam, 0.05% (Desonide Foam) is a petrolatum-based emulsion aerosol foam containing the active ingredient desonide, a low potency corticosteroid for the treatment of atopic dermatitis. The route of administration is topical and the dosing regimen is twice daily for up to four weeks. Desonide Foam is formulated to provide patients with an easily applied product containing [redacted].

The quantitative composition of Desonide Foam is contained in the following Table.

**Quantitative Composition of Desonide Foam 0.05%**

| Component | Reference to Quality Standard | Function | %w/w[1] |
|---|---|---|---|
| [redacted] | | | |
| Desonide | In-house | [redacted] | |
| Propylene Glycol | USP | [redacted] | |
| Phenoxyethanol | NF | [redacted] | |
| [redacted] | | | |
| White Petrolatum | USP | [redacted] | |
| Light Mineral Oil | NF | [redacted] | |
| Isopropyl Myristate | NF | [redacted] | |
| Sorbitan Monolaurate | NF | [redacted] | |
| Ceryl Alcohol | NF | [redacted] | |
| Cyclomethicone | NF | [redacted] | |
| [redacted] | | | |
| Purified Water | USP | [redacted] | |
| Anhydrous Citric Acid | USP | [redacted] | |
| Potassium Citrate (Monohydrate) | USP | [redacted] | |
| Polyoxyl 20 Cetostearyl Ether | NF | [redacted] | |

Desonide Foam is packaged in an aluminum container [redacted] It is supplied in a 100 g size.

6 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

# Individual Study Reviews:

**NDA: 21-978/Study DES.C.201** **Study Dates: Jul, 04 – Oct, 05**

**An Open-Label Study to Evaluate the Safety of Desonide Foam, 0.05%, Including Its Effect on the Hypothalamic Pituitary Adrenal Axis of Adolescent and Pediatric Subjects**

**Objectives:** To evaluate the safety of Desonide Foam including its effect on the hypothalamic pituitary adrenal (HPA) axis following twice daily (morning and evening) application for 4 weeks to the diseased skin of adolescent and pediatric subjects with atopic dermatitis.

**Methodology:** This was a multicenter, open-label study in approximately 60 evaluable adolescent and pediatric subjects with mild to moderate atopic dermatitis to assess the safety of Desonide Foam including its effect on the HPA axis, as measured by the cosyntropin stimulated change in serum cortisol response. Subjects who met all inclusion and exclusion criteria including a clinical diagnosis of mild to moderate atopic dermatitis based on an Investigator.s Static Global Assessment score of 2 or 3, at least 25% treatable body surface area (BSA) involvement and a normal serum cortisol response at Screening were eligible to enter the study. The criterion to establish a normal response was a post-injection serum cortisol level greater than 18.0 mcg/dL.

Number of Subjects Planned: 60 subjects, 15 evaluable subjects per age cohort
Number of Subjects Enrolled: 81 subjects
*Cohort 1*: ≥ 12 years < 18 years.enrolled 19 subjects
*Cohort 2*: ≥ 6 years < 12 years.enrolled 16 subjects
*Cohort 3*: ≥ 3 years < 6 years.enrolled 22 subjects
*Cohort 4*: ≥ 3 months < 3 years.enrolled 24 subjects
Gender: Male: 30 Female: 51
Age: 3 months to 18 years
Ethnicity (Race): Caucasian: 35 , Black: 29, Hispanic: 10, Asian: 5, Other: 2

The study consisted of 4 weeks of treatment with visits at Screening, Baseline, Weeks 1, 2, 4 (or end of treatment) and a Conditional Visit scheduled 4 weeks post-treatment as needed for laboratory testing or adverse experience evaluations. The maximum time a subject could be in the study was 8 weeks if they were required to return for a Conditional Visit. All treatments were administered twice daily (morning and evening) for 4 weeks to a minimum of 25% treatable body surface area (BSA).

At the first visit (Screening) a cosyntropin stimulation test was conducted for each subject to determine the post-injection serum cortisol level and blood was drawn to determine the subject's serum glucose levels. At Visit 1 (Baseline) each subject's

eligibility to participate in the study was evaluated; post-injection serum cortisol levels were reviewed; treatable BSA was assessed to be at least 25%. Subjects eligible for enrollment were instructed by the nurse/study coordinator in the proper use of study medication and drug was dispensed. Subjects/primary caregivers were to apply study drug twice daily (morning and evening) to at least 25% treatable BSA twice daily application for 4 weeks. All areas affected with atopic dermatitis were treated with the study drug, including the face, scalp, and intertriginous areas. In the event of improving or clearing of disease, the subject was to continue to apply study drug to at least 25% BSA.

At Visits 2 and 3 (Weeks 1 and 2) the extent of atopic dermatitis (% BSA), and compliance with study drug were determined.

At Visit 4 (Week 4 or end of treatment) the extent of atopic dermatitis (%BSA), and compliance with study drug were determined. A cosyntropin stimulation test was conducted on each subject to determine post-injection serum cortisol levels and blood was drawn to determine serum glucose levels. Subjects with an abnormal cosyntropin stimulation test at Visit 4, other abnormal laboratory results or study drug related adverse experiences requiring follow-up were scheduled for a Conditional Visit (4 weeks following last study drug administration). At the Conditional Visit, a cosyntropin stimulation test was conducted for subjects with an abnormal serum cortisol level at the previous visit. Blood was drawn for subjects with an abnormal, clinically significant serum glucose level at the previous visit.

Criteria for evaluation: All basal and post-stimulation serum cortisol levels at Screening, Week 4, and Conditional Visit (as applicable) are listed for each subject.
Effect on HPA axis as determined by response to cosyntropin stimulation tests. The criterion to establish a normal response is a post-injection serum cortisol level greater than 18 mcg/dL.

**Results:** Summary of Serum Cortisol (mcg/dL) of all subjects are listed in the following Table 1.

The proportion of subjects determined to have demonstrated HPA axis suppression was 4% (3/75) of subjects overall, 5% (1/18) of subjects in Cohort 1 ($\geq$ 12 < 18 years), 5% (1/20) of subjects in Cohort 3 ($\geq$ 3 < 6 years), and 5% (1/22) of subjects in Cohort 4 ($\geq$ 3 months < 3 years). No subjects in Cohort 2 (>6<12 years) demonstrated any evidence of HPA axis suppression (Table 2).

## Table 1: Summary of Serum Cortisol (mcg/dL)

| | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 | Total |
|---|---|---|---|---|---|
| Number of Subjects | 19 | 16 | 22 | 24 | 81 |
| Basal-Stimulation Levels | 19 | 16 | 22 | 24 | 81 |
| Screening | | | | | |
| n | 19 | 16 | 22 | 24 | 81 |
| mean(std) | 13.67(6.26) | 13.35(5.53) | 13.64(6.22) | 13.63(9.53) | 13.59(7.13) |
| median | 10.60 | 12.35 | 11.55 | 11.90 | 11.80 |
| min, max | (8.0,34.0) | (4.1,24.4) | (4.0,26.7) | (5.0,50.9) | (4.0,50.9) |
| Week 4/ End of Treatment | | | | | |
| n | 19 | 16 | 20 | 23 | 78 |
| mean(std) | 14.12(5.12) | 13.23(6.25) | 12.16(4.23) | 10.99(4.78) | 12.51(5.11) |
| median | 13.10 | 13.00 | 11.25 | 10.00 | 11.90 |
| min, max | (7.3,26.2) | (3.8,22.8) | (5.2,20.8) | (3.8,21.0) | (3.8,26.2) |
| Conditional Visit | | | | | |
| n | 1 | – | 1 | 1 | 3 |
| mean(std) | 14.60(.) | – | 24.40(.) | 8.90(.) | 15.97(7.84) |
| median | 14.60 | – | 24.40 | 8.90 | 14.60 |
| min, max | (14.6,14.6) | – | (24.4,24.4) | (8.9,8.9) | (8.9,24.4) |
| | | | | | |
| Post-stimulation Levels | 19 | 16 | 22 | 24 | 81 |
| Screening | | | | | |
| n | 19 | 16 | 22 | 24 | 81 |
| mean(std) | 26.95(5.55) | 28.43(4.80) | 30.18(5.54) | 33.12(10.64) | 29.95(7.58) |
| median | 26.80 | 28.10 | 29.80 | 30.65 | 29.20 |
| min, max | (21.0,42.0) | (21.3,35.3) | (19.7,44.6) | (19.0,70.8) | (19.0,70.8) |

| | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 | Total |
|---|---|---|---|---|---|
| Week 4/End of Treatment | | | | | |
| n | 19 | 16 | 20 | 20 | 75 |
| mean(std) | 25.03(4.75) | 27.63(4.11) | 28.90(7.80) | 27.97(5.64) | 27.40(5.90) |
| median | 24.20 | 27.05 | 27.55 | 27.95 | 26.60 |
| min, max | (18.0,36.0) | (22.4,36.6) | (16.1,46.3) | (17.5,41.0) | (16.1,46.3) |
| Conditional Visit | | | | | |
| n | 1 | – | 1 | 1 | 3 |
| mean(std) | 20.30(.) | – | 40.60(.) | 30.80(.) | 30.57(10.15) |
| median | 20.30 | – | 40.60 | 30.80 | 30.80 |
| min, max | (20.3,20.3) | – | (40.6,40.6) | (30.8,30.8) | (20.3,40.6) |

Note: If Serum Cortisol measurement is below the undetectable level then the measurement is calculated using

**Table 2: Incidence of (Reversible) HPA Axis Suppression by Cohort**

| | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 | Total |
|---|---|---|---|---|---|
| Number of Subjects | 19 | 16 | 22 | 24 | 81 |
| Week 4/End of Treatment | | | | | |
| n | 19 | 16 | 20 | 20 | 75 |
| HPA Axis Suppression | 1 (5%) | 0 | 1 (5%) | 1 (5%) | 3 (4%) |
| Conditional Visit | | | | | |
| n | 1 | 0 | 1 | 1 | 3 |
| HPA Axis Suppression | 0 | NA | 0 | 0 | 0 |

Note: HPA Axis Suppression defined as a post-injection serum cortisol level oif less than or equal to 18 ug/dL.

In Cohort 1, subject 155-0013 was determined to have demonstrated HPA axis suppression at Week 4 which was reversed at the Conditional Visit. The post-stimulation result at week 4 for subject 155-0013 was 18.0 mcg/dL. At the Conditional Visit, the pre-stimulation level was 14.6 mcg/dL and the post-stimulation level was 20.3 mcg/dL. The subject was an otherwise healthy, 16-year-old female who weighed 122.8 lbs. Her initial % BSA was 28%.

In Cohort 3, subject 176-0009 was determined to have demonstrated HPA axis suppression at Week 4 which was reversed at the Conditional Visit. The subject was an otherwise healthy, 4-year-old male who weighed 40.0 lbs. The post-stimulation value at week 4 for subject 176-0009 was 16.2 mcg/dL and the post-reading was 16.1 mcg/dL. At the Conditional Visit, the pre-stimulation level was 24.4 mcg/dL and the post-stimulation level was 40.6 mcg/dL. His initial BSA was 34%.

In Cohort 4, subject 176-0010 was determined to have demonstrated HPA axis suppression at Week 4 which was reversed at the Conditional Visit. The subject was an otherwise healthy, 2 year old male who weighed 31.0 lbs. The post-stimulation result at week 4 for subject 176-0010 was 17.5 mcg/dL. At the Conditional Visit, the pre stimulation level was 8.9 mcg/dL and the post-stimulation level was 30.8 mcg/dL. The subject suffered from occasional fevers during the study which might have been a secondary cause of the mild suppression. His initial BSA was 30%.

**Conclusion:** 3 of 75 evaluable subjects experienced HPA axis suppression at Week 4 as determined by a post-cosyntropin stimulation serum cortisol level of 18 mcg/dL or less and all had a reversal of their serum cortisol levels at a Conditional Visit scheduled for 4 weeks after suppression was observed. Therefore the following section should be added in the Pharmacokinetics section of the PPI.

**Pharmacokinetics:**

*Treatment beyond 4 consecutive weeks is not recommended, because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. In a controlled pharmacokinetic study, 3 of 75 (4%) patients experienced* [redacted] *suppression of the adrenal following 4 weeks of* [redacted] *(desonide) Foam therapy.*

**NDA: 21-978/Study DES.C.102** **Study Dates: Dec' 04 – Apr' 05**

**A Single-blind, Single Exposure Study, to Evaluate the Vasoconstriction Activity of Topically Delivered Desonide Foam, 0.05% in Normal Skin in Healthy Adult Subjects: Dose Ranging Study**

**Objective of the Study:**

**Part A:** Validate vasoconstrictor assay precision.
**Part B:** To evaluate the dose response vasoconstriction profile of Desonide Foam, 0.05%, (Desonide Foam) at different dose durations over a short period of time (15 min – 6 hrs).

**Study Design:** This was a single-blind, single-exposure study on healthy adult male and female subjects. Potential subjects were screened for vasoconstriction responsiveness using two dose applications of Desonide Foam (20 µL to 4 $cm^2$ ; one occluded and one non-occluded) on normal skin of the upper ventral arms (two sites). For Part A of the study conduct, six subjects had four 4-$cm^2$ untreated sites on one forearm measured by Chromameter™ to assess reproducibility and precision of the test facilities technique and instrumentation. Individuals that met all inclusion and exclusion criteria and demonstrated a visual vasoconstriction score of 1 or greater at both screen test sites were qualified for enrollment into the. For Part B of the study conduct, 12 subjects had eight 4-cm2 sites on both forearms evaluated for vasoconstriction response to a single lot of Desonide Foam following different durations of dose application ranging from 15 minutes to 6 hours. Two untreated sites on each arm remained as control sites. Both arms were dosed identically. On one arm, all test sites were occluded, while on the other arm, the test sites remained non-occluded. Vasoconstriction response was evaluated by Chromameter measurement at pre-dose, 1, 2, 4, 6, 8, 10, 20, 24, 28, and 32 hours after dose removal, for a total of 11 time points. This study was based on the staggered application and synchronized removal dose-duration response study design.

Degree of vasoconstriction response (skin blanching) was conducted visually at the Screening phase only and scored on a five-point scale (0 to 4). In the Treatment phase, skin blanching was conducted by the use of a ' ) using the L*A*B color scale ("a" value only).

Chromameter "a" scores (L*A*B scale) were tabulated, corrected for baseline readings and then corrected for the untreated sites at each time point. Descriptive statistics were obtained and differences between dose durations as well as determination of $ED_{50}$, $E_{max}$, and $AUEC_{(0-24)}$ values for both occluded and non-occluded arms, were made using population based ANOVA methods (SAS and P-Pharm software).

**Results:**

**Part A:** Five repetitive Chromameter measurements were conducted on four non-dosed sites on six subjects within a one-hour duration. Overall coefficient of variation was determined to be 7.33% across non-dosed sites and subjects.

**Part B**: The calculated $AUEC_{(0-24)}$ results are presented below:

**Summary Chromameter Negative $AUEC_{(0-24h)}$ Results (mean; n = 12)**

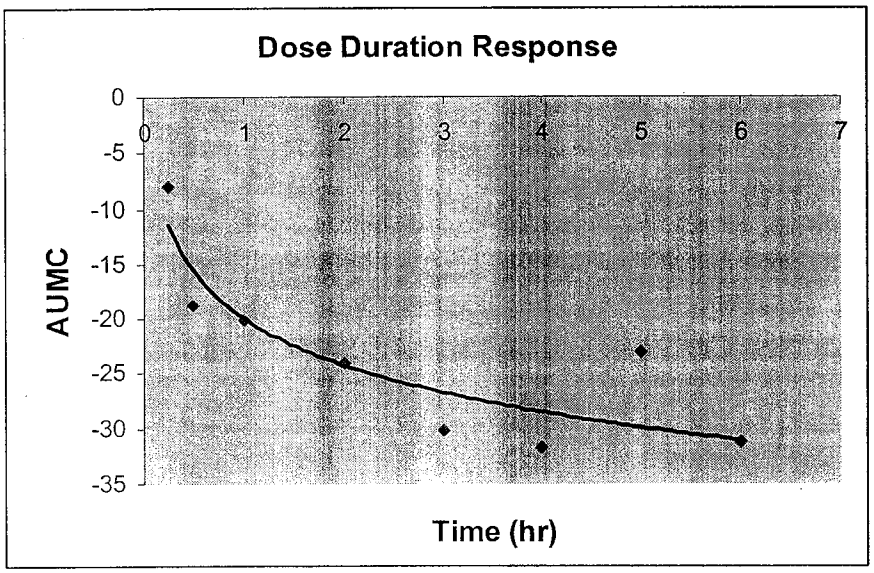
| Formulation | Dose Duration (hr) | Occluded Sites Negative $AUEC_{0-24h}$ | Non-Occluded Sites Negative $AUEC_{0-24h}$ |
|---|---|---|---|
| Desonide Foam, 0.05% | 0.25 | 8.1 | 2.0 |
| Desonide Foam, 0.05% | 0.5 | 18.7 | 20.9 |
| Desonide Foam, 0.05% | 1 | 20.2 | 9.6 |
| Desonide Foam, 0.05% | 2 | 24.1 | 17.9 |
| Desonide Foam, 0.05% | 3 | 30.3 | 5.0 |
| Desonide Foam, 0.05% | 4 | 31.8 | 18.7 |
| Desonide Foam, 0.05% | 5 | 23.0 | 15.8 |
| Desonide Foam, 0.05% | 6 | 31.3 | 20.9 |

**Summary $ED_{50}$ and $E_{MAX}$ Results from P-Pharm Statistical Analysis**

| Treatment | # Subjects* | $ED_{50}$ | $E_{max}$ |
|---|---|---|---|
| Occluded | 11 | 0.25 hr | 32 |
| Non-Occluded | 11 | na | na |
| Occluded | 12 | 0.24 hr | 29 |
| Non-Occluded | 12 | na | na |

* With and without Subject #008 who had an abnormal (+ 0.15) reading at the Hour 6 reading.

The dose-response effect based on vasoconstrictor results obtained from the subjects was used for estimation of the $ED_{50}$ and Emax values from only the occluded test sites. The data from the non-occluded sites, across subjects, could not provide an $ED_{50}$ estimate due to the low vasoconstriction response measured and the high degree of variability seen from the response that could be measured. Statistical evaluation of the $AUEC_{0-24h}$ dose duration data from the occluded sites suggests an $ED_{50}$ of about 0.25 hours (Figure below).




However, given the low vasoconstriction response observed at 0.25 hr, the Principal Investigator recommends that, for a pivotal potency ranking study, the $ED_{50}$ for the foam formulation containing desonide be tested at a dose duration no less then 0.25 hrs, and no greater than 1 hr, with the test sites occluded during the dose application period.

**Comment:** *Based on the study result, the reviewer concurs with the principal investigator's recommendation that the final to be marketed desonide foam formulation should be tested around dose duration of one hour under occlusion in the pivotal study. In fact, the pivotal study was conducted at dose duration of one hour under occlusion.*

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**NDA: 21-978/Study DES.C.101** **Study Dates: Apr, 05 – May, 05**

**A Skin Blanching Study of Desonide Foam, 0.05% by Human Vasoconstrictor Assay**

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**Objective of the Study**: The objective of this study was to compare the relative vasoconstrictor potency of Desonide Foam, 0.05% (Desonide Foam) to: 1) Elocon® cream, 0.1%, 2) hydrocortisone cream 0.5%, 3) Tridesilon® cream, 0.05% and 4) Vehicle Foam.

**Study Design:** This single center, masked (evaluator and subject) study was designed to compare the vasoconstriction effect of a new foam based Desonide formulation to three other commercially available topical corticosteroid formulations: Elocon Cream (0.1% mometasone furoate), Tridesilon Cream (0.05% Desonide) and hydrocortisone Cream 0.5% in 36 (11M; 25F; 34 Caucasian; 1 Hispanic; 1 Asian) healthy volunteers. Potency was assessed using the vasoconstriction response of the skin following a 1 (one) hour

occluded dose exposure duration to each formulation as measured using the chromometer. The selection of the dose duration and the use of occlusion was based on information obtained from a previously conducted pilot study, DES.C.102.

At the Screening visit, an assessment of the skin on the subjects' forearms was conducted. A test area (4 $cm^2$) was demarcated on normal skin on the upper ventral arm of each subject and a pre-dose visual assessment was conducted. Tridesilon cream (20 µL) was applied to the designated test area and covered with an occlusive dressing. Removal of Tridesilon cream occurred 5.5 hours following application. A visual score assessment was performed 30 minutes after dose removal to evaluate skin blanching response. A visual skin blanching score of 1 (one) or greater qualified the subject for inclusion into the study.

During the evaluation phase, subjects were instructed to: shower no less than 2 hours before test article administration (Day 1); refrain from using lubricating creams on the forearms for 24 hours prior to Day 1 and throughout the study; not to exercise, bathe, or shower during the study (Day 1–2). Subjects were permitted to leave the clinic with test articles in place on the Screening Day provided they agreed not to disturb the test sites, wash, or bathe, or perform any activities that would induce sweating. At Day 1, a total of seven test sites (4 $cm^2$) were demarcated on each forearm. Following pre-dose chromameter readings of all test sites, 20 µL of each test article was applied to a test site on each forearm (five applications per arm). Two other sites on each forearm remained untreated and served as control sites (total of 4 control sites). All test sites (treated or untreated) were occluded. Test articles were removed 1 hour after application. Sites remained un-occluded after test article removal. Chromameter assessment of all test sites was conducted at 1, 2, 4, 6, 8, 10, 12, 24, 27, 30, and 36 hours after test article removal (a total of 11 time points post-dose removal).

**Results:**

**Assay Validation:** To validate the precision of the vasoconstrictor assay, five repetitive chromameter measurements were conducted on four non-dosed sites on six subjects within a one-hour duration. Overall coefficient of variation was determined to be 4.23% across sites and subjects.

**Vasoconstriction Response:**The vasoconstriction responses detected were consistent for the topical application of corticosteroids versus the control sites. Specifically, the non-dosed control sites and the Foam vehicle (placebo) dosed sites demonstrated no vasoconstriction response. Those sites that received the hydrocortisone cream 0.05% formulation also did not demonstrate any measurable vasoconstriction response across subjects as expected from topical hydrocortisone formulations as well as for other low potency ranked topical corticosteroid formulations. Expectedly, the Desonide and Elocon formulations demonstrated graded vasoconstriction responses. The mean negative AUEC results and statistical comparisons are provided in the following Table.

**Mean –AUEC and Statistical Grouping using the Tukey's Studentized Range Test (Means with the same group letter are not significantly different)**

| Formulation | –AUEC | N | Grouping | Grouping |
|---|---|---|---|---|
| Desonide Foam 0.05% | 19.406 | 72 | A | |
| Tridesilon Cream 0.05% | 13.736 | 72 | A | B |
| Elocon Cream 0.1% | 9.364 | 72 | | B |
| Control | 0.020 | 144 | C | |
| Vehicle Foam | –0.708 | 72 | C | |
| Hydrocortisone Cream 0.05% | –0.727 | 72 | C | |

The statistical analysis indicates that there is no significant difference in the vasoconstriction response between the Tridesilon Cream (0.05% Desonide) and the new Desonide Foam 0.05% formulation. This suggests that these two formulations should be considered within the same potency category (generally recognized as "mild" or"low" potency). Elocon (0.1% mometasone furoate) which is generally recognized as a "moderate" potency formulation, and thus by inference, would produce a greater vasoconstriction response over Desonide, did, in this study, demonstrate a lower AUEC, but statistically similar response to the Tridesilon Cream.

**Discussion:** According to the sponsor, the disparity in the Elocon response (verses its recognized potency ranking) is most likely attributable to the applied dose duration and occlusion of the applied dose. The original potency ranking of Elocon was most likely made using visual scoring, a non-occluded dose, and evaluated using the older McKenzie-Stoughton assay approach which calls for a 16-hour dose duration. It is very likely that the delivery and percutaneous absorption characteristics of mometasone furoate would be quite different under a 1-hour occlusive dose (this study design) versus a 16-hour non-occlusive dose; consequently, a different vasoconstriction response would be similarly likely to have occurred. However, this study was designed to compare various formulations under identical conditions that were chosen to match the $ED_{50}$ established for Desonide Foam in the pilot study, DES.C.102. Based on the statistical similarity between the Desonide Foam and the Tridesilon Cream, these two formulations should be considered similar in ranking potency (i.e., low potency).

***Comment:*** *As Desonide Foam and the Tridesilon Cream show statistical similarity in skin blanching, these two formulations should be considered similar in ranking potency.*

## *Office of Clinical Pharmacology and Biopharmaceutics*

# *New Drug Application Filing and Review Form*

**General Information About the Submission**

| | Information | | Information |
|---|---|---|---|
| NDA Number | 21-978 | Brand Name | Foam |
| 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%) Foam |
| | | Dosing Regimen | BID |
| Date of Submission | 11/18/05 | Route of Administration | Topical |
| Estimated Due Date of OCPB Review | 06/18/06 | Sponsor | Connectics |
| PDUFA Due Date | 09/18/06 | 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 | 2 | | |
| *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 | | 3 | | |
| | | | | |

| 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 12-14-05* | |
| Secondary reviewer Signature and Date | | |

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/
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