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APPLICATION NUMBER:

204141Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204141	Submission Date(s): 6/12/2012, 6/22/2012, 7/16/2012, 7/23/2012, 8/6/2012
Brand Name	Topicort
Generic Name	Desoximetasone 0.25%
Primary Reviewer	An-Chi Lu, M.S., Pharm.D.
Team Leader	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Taro Pharmaceuticals USA Inc
Submission Type; Code	Original NDA
Formulation; Strength(s)	Topical spray 0.25%
Indication	Moderate to severe plaque psoriasis in patients 18 years of age or older

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1 Executive Summary

This application is for Topicort® (Desoximetasone) Spray, 0.25%. The proposed indication for Topicort® Spray is topical treatment of [redacted] (b) (4) plaque psoriasis in patients 18 years of age or older. The spray is intended to be applied a thin film to the affected skin areas twice daily. In the US, desoximetasone is commercially available in 0.05% and 0.25% strength as ointment, cream, and gel, such as Topicort ® 0.05% Ointment (NDA #018594), Topicort ® 0.25% Cream (ANDA #073193), Topicort® 0.05% Cream (ANDA #073210), Topicort® 0.25% Ointment (ANDA #074286), and Topicort® 0.05% Gel (ANDA #074904).

To support the NDA, the sponsor has submitted the following Clinical Pharmacology trials: a) vasoconstriction trial b) systemic safety hypothalamic-pituitary-adrenal (HPA) axis suppression trial in adult subjects with moderate to severe plaque psoriasis.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 204141 acceptable from a Clinical Pharmacology perspective, pending agreement on recommended labeling changes and the post marketing requirements outlined in section 1.2 of this review.

1.2 Phase IV Commitments/Requirements

Post Marketing Requirement (PMR) for a safety trial to evaluate HPA axis suppression and pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment in subjects age 2-16 years and 11 months with psoriasis. The trial should be conducted in sequential cohorts:

Cohort 1: age 12 years to 16 years 11 months
Cohort 2: age 6 years -11 years and 11 months
Cohort 3: age 2 years to 5 years and 11 months

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

HPA Axis Suppression:

The HPA axis testing in Trial DSXS 0805 was conducted with multiple dosing with Desoximetasone Spray, 0.25% in subjects with moderate to severe plaque psoriasis. Twenty-four (24) subjects 18 years of age or older with a confirmed diagnosis of moderate to severe plaque psoriasis with a Physicians Global Assessment (PGA) score of 3 (moderate) or 4 (severe) for the overall disease severity, 12 having involvement of 10-15% of their body surface area and 12 having involvement of > 15% of their body surface area were enrolled. Desoximetasone spray, 0.25% was applied gently and completely rubbed in to the affected areas twice a day (morning and evening) for 28 days. Plasma desoximetasone concentrations were tested at baseline (Visit 1), Day 14 (Visit 4), and Day 28 (Visit 5). At Visit 5 (Day 28) patients underwent the final cortisol response test to assess HPA axis function after treatment with Desoximetasone Spray, 0.25%.

For the results of cortisol concentrations, data from 3 local laboratories were used. Because one of the laboratory failed to submit the quality control results during similar time frame the trial was conducted, the cortisol data from 3 patients (all in the group with >15% BSA affected) analyzed at this laboratory were removed from the HPA axis suppression result.

According to FDA's criterion, subjects are considered normal and showed no evidence of any abnormal HPA function or adrenal response in a cortisol response test if response to cosyntropin stimulation is >18 µg/dL 30 minutes after stimulation. The results showed that 3 out of 21 patients or 14% met the criterion for adrenal suppression. Among the 3 patients, 1 out of 12 patient (8%) is in the group with 10-15% BSA affected and 2 out of 9 patients (22%) are in the group with >15% BSA affected.

Pharmacokinetics:
Three pharmacokinetic (PK) samplings were collected in all subjects, one at baseline and one on each Day 14 and Day 28, at least 8 hours after dosing. The mean (% Coefficient of Variation) concentration of desoximetasone was 449 pg/mL (86%) at Day 14 and 678 pg/mL (135%) at Day 28. However, there were only single PK samplings on Day 14 and 28, and the full PK profile following application of desoximetasone spray, 0.25% was not evaluated and is not known.

Vasoconstrictor Trial:
A vasoconstriction trial (10715005) was conducted to determine the relative vasoconstrictive potency of desoximetasone spray, 0.25% formulation compared to a placebo spray (vehicle), and seven other marketed corticosteroid formulations of known potency. The degree of vasoconstriction was assessed using a single timepoint visual scoring as well as using a single timepoint ChromaMeter (a-scale reading) assessment two hours after product removal.

Based on the visual scoring data, the skin blanching response of desoximetasone spray, 0.25% was not significantly different from clobetasol propionate 0.05% spray (Class 1), mometasone furoate 0.1% ointment (Class 2), desoximetasone 0.25% cream (Class 2), and fluocinonide 0.05% ointment (Class 2), and was significantly different from fluticasone propionate 0.05% cream (Class 5), and hydrocortisone 2.5% cream (Class 7). The fact that there is no statistically significant difference between Topicort® Spray, 0.25% and products of Class 1 and 2 does not support the applicant's conclusion of classifying Topicort® Spray 0.25% as a super-high potency steroid. This reviewer recommends that Topicort® Spray, 0.25% should be classified as a Class 1/2 potency steroid, instead of a Class 1 super high potency steroid.

Pediatrics:
The applicant requested a waiver of pediatric trials (b) (4) Both Division of Dermatology and Dental Products (DDDP) and Pediatric and Maternal Health Staff (PMHS) did not agree with the applicant's requested waiver. DDDP recommended the applicant to conduct a safety trial to evaluate HPA axis suppression as well as pharmacokinetics of desoximetasone (recommended by clinical pharmacology) under maximal use conditions after 4 weeks of treatment in subjects age 2-16 years and 11 months with psoriasis. The trial should be conducted in sequential cohorts. A minimum of 30 evaluable subjects should be enrolled in each cohort:

Cohort 1: age 12 years to 16 years 11 months
Cohort 2: age 6 years -11 years and 11 months
Cohort 3: age 2 years to 5 years and 11 months

Approximately 2% of pediatric subjects with psoriasis are less than 2 years of age. Thus, the evaluation of pediatric subjects less than 2 years of age is waived.

This recommendation was agreed by the Pediatric Review Committee (PeRC) at the meeting on January 9, 2013.

Clinical Pharmacology Briefing:
An optional intra-division level Clinical Pharmacology briefing was conducted on January 14, 2013 with the following in attendance: Doanh Tran, E. Dennis Bashaw, Chinmay Shukla, and An-Chi Lu.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the proposed indication for Desoximetasone Spray, 0.25%?

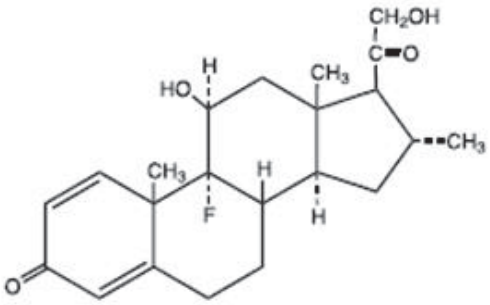
Desoximetasone Spray, 0.25% is proposed for the treatment of (b) (4) plaque psoriasis in patients 18 years of age and older.

2.1.2 What is plaque psoriasis?

Psoriasis is a chronic disorder with polygenic predisposition combined with triggering environmental factors such as trauma, infection, or medication. Most common sites of involvement are scalp, elbows, knees, hands, feet, trunk, and nails. Pathology is characterized by uniform elongation of the rete ridges, with dilated blood vessels, thinning of the suprapapillary plate, and intermittent parakeratosis. Epidermal and perivascular dermal infiltrates of lymphocytes, with neutrophils occasionally in aggregates in the epidermis.
Plaque psoriasis (psoriasis vulgaris) is one of the forms with 80-90% of patients with psoriasis. It is characterized by small, red bumps that enlarge, become inflamed, and form scales. The top scales flake off easily and often, but those beneath the surface of the skin clump together. Removing these scales exposes tender skin, which bleeds and causes the plaques (inflamed patches) to grow.

2.1.3 What are the highlights of the physicochemical properties of Desoximetasone?

Chemically, desoximetasone is Pregna-1, 4-diene-3, 20-dione, 9-fluoro-11, 21-dihydroxy-16-methyl-, (11ß,16α)-.
It has the following structural formula:



Desoximetasone has the molecular formula $C_{22}H_{29}FO_4$ and a molecular weight of 376.47.
The CAS Registry Number is 382-67-2.

Formulation properties:
It is a non-aqueous spray formulation. It is delivered with a spray pump to allow more convenient application of the product, with each (b) (4) spray delivering (b) (4) of desoximetasone, USP.
Formulation of 0.25% (w/w) spray containing desoximetasone is provided below:

Table 1: Desoximetasone Spray, 0.25% Quantitative Composition and Functions of Ingredients.

Component and Quality Standard	Quantity per unit (mg/g)	% (w/w)	Functions of Ingredients
Desoximetasone, USP	2.5	0.25	Active ingredient
Glyceryl Oleate, Taro	(b) (4)	(b) (4)	(b) (4)
Isopropyl Alcohol, USP			
Isopropyl Myristate, NF		(b) (4)	
L-Menthol, USP			
Mineral Oil, USP			
Total Weight		100%	

USP = United States Pharmacopoeia.

Dosage and Route of Administration:
Apply a thin film to the affected skin areas twice daily. This usage is consistent with the other approved Topicort® products with the same strength (0.25% cream and ointment).

Mechanism of Action:
Corticosteroids play a role in cellular signaling, immune function, inflammation and protein regulation; however, the precise mechanism of action in psoriasis is unknown.

2.2 General Clinical Pharmacology

2.2.1 How was the dose/duration selected for Desoximetasone spray, 0.25%?

The recommended dosage of Desoximetasone Spray, 0.25% is one application (a thin film) twice daily. In the proposed labeling, Desoximetasone Spray, 0.25% is instructed to be sprayed directly onto the affected skin areas and rubbed in gently. As with other corticosteroids, therapy should be discontinued when control of psoriasis is achieved.
In the current submission, the above dosing regimen was determined in the Phase 2 dose-finding trial DSXS-0906. This trial evaluated two dosing regimens (once or twice a day) of two strengths of Desoximetasone Spray (0.05% and 0.25%). There were two efficacy endpoints. The primary endpoints were the proportion of patients in each treatment group who were considered a Clinical Success (PGA score of 0 or 1) at Day 28 (or early termination) and the proportion of patients in each treatment group who were considered a Treatment Success for the target lesion (a score of 0 or 1 for each of the three signs/symptoms (i.e., scaling, erythema and plaque elevation) at Day 28 (or early termination). The second endpoints were the mean change from baseline in PGA score at Day 28, the mean change from baseline in PGA score at Day 28, the mean change from baseline in the TLSS (Total Lesion Severity Score) at Day 28 (or early termination) and the mean change from baseline in %BSA affected at Day 28 (or early termination).
It was concluded that Desoximetasone spray 0.25% was statistically significantly superior to vehicle for both primary endpoints. The 0.05% formulation of desoximetasone spray did not demonstrate superiority over vehicle for any of the endpoints evaluated. In direct comparisons of once-a-day versus twice-a-day application of the 0.25% formulation of desoximetasone spray there were no significant differences for either the primary or secondary endpoints. The sponsor decided to use the twice-a-day application of the 0.25% formulation of desoximetasone spray for the subsequent phase III efficacy trial in patients with moderate to severe plaque psoriasis based on the results of the superiority to vehicle analysis.

2.2.2 What are the design features of the clinical pharmacology and clinical trials used to support Desoximetasone spray, 0.25%?

The applicant has sponsored the following eight clinical trials in support of the development of Desoximetasone Spray, 0.25%:

Clinical Pharmacology Trials (Phase I Trials):
Vasoconstriction trial 10715005: Vasoconstrictor assay in healthy adult subjects (N = 32, Aged 18-47 years old).

DSXS-0804: Cumulative Irritation/Sensitization multiple-site, within-subject, randomized trial in healthy adult subjects (N = 297, Aged 18-67). The medical reviewer is reviewing this trial.

DSXS-0805: Systemic safety HPA axis suppression trial in adult subjects with moderate to severe plaque psoriasis (N = 24, Aged 18-74). Desoximetasone spray, 0.25% was applied twice a day for 28 days.

DSXS-0904: Phototoxicity trial in healthy subjects (N = 38, Aged 23-70). Desoximetasone 0.25%, 0.05%, and the vehicle spray were applied to the back for 24 hours, and then exposed to irradiation. The medical reviewer is reviewing this trial.

DSXS-0905: Photoallergy trial in healthy subjects (N = 58, Aged 20-70). Desoximetasone 0.25%, 0.05%, and the vehicle spray were applied to the back for 24 hours, and then exposed to irradiation. These procedures were performed twice weekly over a 3-week induction period. The medical reviewer is reviewing this trial.

Phase II trials:
DSXS-0906: Dose-finding trial (N = 150, Aged 22-82) to evaluate two dosing regimens (once or twice a day) of two strengths of Desoximetasone Spray (0.05% and 0.25%) for 28 days. Patients with moderate to severe plaque psoriasis were randomly assigned in a 2:2:2:2:1:1 ratio to one of six treatment regimens.

Phase III trials:
Two replicate trials with identical designs were conducted (DSXS-0808 and DSXS-0914). Both were double-blind, vehicle-controlled, randomized, parallel group, multiple-site trial comparing desoximetasone spray, 0.25% with a vehicle control spray in patients with moderate to severe plaque psoriasis. Study drug was applied to affected areas twice a day for 28 days. The medical reviewer is reviewing these two trials.

2.2.3 What are the effects of desoximetasone spray, 0.25% on HPA axis suppression?

The systemic exposure and potential for adrenal suppression of Desoximetasone 0.25% topical spray was evaluated in trial DSXS-0805. Trial 0805 was an open label, safety/efficacy trial to assess the potential for adrenal suppression following multiple dosing with desoximetasone spray, 0.25% in patients with moderate to severe plaque psoriasis. Twenty-four (24) patients 18 years of age or older with a confirmed diagnosis of moderate to severe plaque psoriasis with a Physicians Global Assessment (PGA) score of 3 (moderate) or 4 (severe) for the overall disease severity, 12 having involvement of 10-15% of their body surface area and 12 having involvement of > 15% of their body surface area were enrolled. Desoximetasone spray, 0.25% was applied twice daily for 28 days. 3 PK samplings were collected in all subjects, one at baseline (Visit 1) and one on each Day 14(Visit 4) and Day 28 (Visit 5), at least 8 hours after dosing. At Visit 5 (Day 28) patients underwent the final cortisol response test to assess HPA axis function after treatment with Desoximetasone.
The sponsor set the following criteria (all 3 criteria must be met) to be considered normal and showed no evidence of any abnormal HPA function or adrenal response in a cortisol response test:

- The basal (pre-Cortrosyn™ injection) cortisol concentration was ≥ 5 mcg/100mL
- Their 30 minute post-injection cortisol level was at least 7 mcg/100 mL greater than the basal level (≥ basal value +7)
- The post stimulation level was > 18 mcg/100 mL

For the cortisol concentration results, data from 3 local laboratories were used. However, because the lab of [redacted] (b) (4) failed to submit quality control results during similar time frame of this trial, the cortisol data of 3 patients (Subject number 03-300, 03-301, and 03-302, all in the group with >15% BSA affected) are removed from the HPA axis suppression discussion and result in this review.

According to sponsor's criteria, the patients who were identified to have adrenal suppression are shown in the table below. A total of 4 out of 21 patients or 19% had a serum cortisol concentration at Day 28 that met at least one of the criteria for adrenal suppression. Among the 4 patients, 2 out of 12 patients (17%) are in the group with 10-15% BSA affected and 2 out of 9 patients (22%) are in the group with >15% BSA affected.

The sponsor's criteria are different from the single criterion of response to cosyntropin stimulation of >18 µg/dL 30 minutes after stimulation recommended by the Agency. If using the FDA's single criterion, 3 out of 21 patients or 14% met the criterion for adrenal suppression (shown in Bold and Italic font in Table 2). Among the 3 patients, 1 out of 12 patient (8.3%) is in the group with 10-15% BSA affected and 2 out of 9 patients (22.2%) are in the group with >15% BSA affected.

Among the 4 patients identified to have adrenal suppression according to sponsor's criteria, 3 patients had post-treatment follow-up with suppression reversed 28 days after the end of treatment. The other 1 patient did not return for follow-up.

Table 2: Cortisol Response Test Results of Patients Identified to Have Adrenal Suppression by Sponsor's Criteria (4 Patients) or FDA's criteria (3 Patients in Bold)

		Visit 1			Visit 5			Follow-up		
Subject number	Group	Basal	Post Inj.	Change from Basal	Basal	Post Inj.	Change from Basal	Basal	Post Inj.	Change from Basal
02-203	***2***	***12.1***	***32.2***	***20.1***	***4.2****	***17.9****	***13.7***	***9.8***	***23.5***	***13.7***
02-211	***2***	***11.2***	***20.3***	***9.1***	***6.4***	***17.9****	***11.5***	***10.3***	***18.7***	***8.4***
02-212	***1***	***10.6***	***18.5***	***7.9***	***5.3***	***17.9****	***12.6***			
02-226	1	9.5	23.9	14.4	4.6*	22	17.4	14.8	25.6	10.8

2.2.4 What is the systemic bioavailability of desoximetasone spray, 0.25%?

The systemic bioavailability of desoximetasone spray, 0.25% was evaluated in trial DSXS-0805 (For the design feature, see Section 2.2.3). The mean (%CV) concentration of desoximetasone was 449 pg/mL (86%) at Day 14 and 678 pg/mL (135%) at Day 28. The sponsor concluded that plasma desoximetasone concentrations were higher in the subjects with HPA axis suppression as compared to other subjects (grouped by BSA affected by psoriasis), as shown in Table 3, although the differences observed did not achieve statistical significance. *However, patients' plasma desoximetasone concentrations were tested at baseline, Day 14, and Day 28 with unspecified time post dose. Therefore, without full PK profile, no definitive conclusion can be drawn to correlate the plasma drug levels to patients with or without HPA axis suppression.*

Table 3: Desoximetasone Plasma Concentrations after 28 Days of Application: Subjects with HPA Axis Suppression versus Those with Normal Cortisol Response

Group	N	Mean ± SD (pg/mL)
10-15% BSA Affected		
Suppression	2	525.37 ± 323.16
No suppression	10	244.93 ± 220.66
>15% BSA Affected		
Suppression	3	1861.51 ± 2222.64
No suppression	9	647.65 ± 503.24

Source: Sponsor Table 2.5:6
BSA=body surface area; LOQ=limit of quantitation

Table 4: Desoximetasone Plasma Concentrations after 14 and 28 Days of Application

Patient Group	Mean Plasma Concentrations Excluding Patients with Values <LOQ[1,2]			Mean Plasma Concentrations Including Patients with Values <LOQ[3]		
	N	Mean ± SD (pg/mL)	P-value	N	Mean ± SD (pg/mL)	P-value
Day 14						
Group 1 (10-15% BSA affected)	10[1]	358.95 ± 180.49	0.4276	11[4]	326.32 ± 202.56	0.4517
Group 2 (>15% BSA affected)	10[2]	507.30 ± 540.12		12	449.89 ± 511.55	
Day 28						
Group 1 (10-15% BSA affected)	10[2]	350.01 ± 228.41	0.1090	12	291.67 ± 247.48	0.0817
Group 2 (>15% BSA affected)	12	951.12 ± 1176.34		12	951.12 ± 1176.34	

Source: Sponsor Table 2.5:2
BSA=body surface area; LOQ=limit of quantitation
[1]Two patients omitted from analysis (one patient had a blood level of desoximetasone below the limit of quantitation and no sample was available for the other patient)
[2]Two patients omitted from analysis (both patients had a blood level of desoximetasone below the limit of quantitation)
[3]Values calculated independently from study report from data given in Sponsor Appendix 16.2.5
[4]One patient omitted from analysis, as no blood sample was obtained

2.2.5 *What is the potency classification of desoximetasone spray, 0.25% based on vasoconstrictive assay?*

A vasoconstriction trial (10715005) was conducted to determine the relative vasoconstrictive potency of a new desoximetasone spray, 0.25% formulation compared to a placebo spray (vehicle), and seven other marketed corticosteroid formulations of known potency. The degree of vasoconstriction was assessed using a single timepoint visual scoring as well as using a single timepoint ChromaMeter (a-scale reading) two hours after product removal. The potency rankings according to visual assessment results are shown in Table 5.

Table 5: Mean Visual Results in Order of Most to Least Potent

	Formulations	N	Mean (16 Hr Duration)	REGWQ Grouping*
Reference Product 3	Fluocinonide 0.05% Ointment, Taro Pharmaceuticals Inc., Lot No. J7106, Expiration Date 10/10 (Class 2)[a]	32	1.3125	A
Reference Product 2	Topicort® (desoximetasone) 0.25% Cream, Taro Pharmaceuticals Inc., Lot No. H7062, Expiration Date 08/10 (Class 2)	32	1.2969	A
Reference Product 4	Elocon® (mometasone furoate) 0.1% Ointment, Schering Corporation, Lot No. 6-UHK-2, Expiration Date 12/08 (Class 2)	32	1.1563	A
Test Product 1	Desoximetasone 0.25% Topical Spray, Taro Pharmaceuticals Inc., Lot No. L163-57868, Manufacture Date 09/06/07	32	1.1563	A
Reference Product 1	Clobex® (clobetasol propionate) 0.05% Spray, Manufactured by CPL, Marketed by Galderma Laboratories Inc., Lot No. 47570, Expiration Date 11/08 (Class 1)	32	1.1094	A
Reference Product 5	Topicort® LP (desoximetasone) 0.05% Cream, Taro Pharmaceuticals Inc., Lot No. 07076, Expiration Date 04/09 (Class 3 or 4)[b]	32	0.9375	B A
Reference Product 6	Cultivate® (fluticasone propionate) 0.05% Cream, Pharma Derm, a Division of Altana Inc., Lot No. Z150, Expiration Date 07/09 (Class 5)	32	0.6406	B
Test Product 2	Desoximetasone (placebo) 0.25% Spray, Taro Pharmaceuticals Inc., Lot No. L163-58081, Manufacture Date 01/16/08	32	0.2344	C
Reference Product 7	Hytone® (hydrocortisone) 2.5% Cream, Dermik Laboratories, a Division of Aventis Pharmaceuticals Inc., Lot No. JE0012, Expiration Date 03/09 (Class 7)	32	0.0156	C
Untreated Site	N/A	32	0.0000	C

*Products with the same Ryan-Einot-Gabriel-Welsh Multiple Range Test (REGWQ) grouping letter are not significantly different.

a. Fluocinonide 0.05% ointment is classified as a Class 1 by the applicant, but is classified as a Class 2 potency steroid according to both the National Psoriasis Foundation and the corticosteroid classification in "Corticosteroid classes: A quick reference guide including patch test substances and cross-reactivity, Jacob and Steele, *J Am Acad Dermatol, April 2006*; 723-727".

b. Topicort® LP (desoximetasone) 0.05% cream is classified as a Class 3 by the applicant, and is also classified as a Class 3 by the National Psoriasis Foundation. However, it is classified as a Class 4 according to the corticosteroid classification in

"Corticosteroid classes: A quick reference guide including patch test substances and cross-reactivity, Jacob and Steele, *J Am Acad Dermatol, April 2006*; 723-727".

The applicant used both ChromaMeter assessment and visual assessment to evaluate the potency ranking; however, we typically rely on visual assessment for the reported values on blanching scoring. The fact that there is no statistically significant difference between Topicort® Spray, 0.25% and products of Class 1 and 2 does not support the applicant's conclusion of classifying Topicort® Spray 0.25% as a super-high potency steroid. This reviewer believes Topicort® Spray, 0.25% should be classified as a Class 1/2 potency steroid, instead of a Class 1 super high potency steroid.

2.2.6 Does Desoximetasone spray, 0.25% prolong QT intervals?

The effects of desoximetasone spray, 0.25% on QT interval have not been evaluated in clinical trials for Desoximetasone spray, 0.25%. The applicant cited that with all the approved desoximetasone products, there was no adverse effect of desoximetasone on ECG parameters reported in the post-marketing safety database from 1977 to 9/30/2011.

2.3 Intrinsic Factors

2.3.1 What is the systemic drug exposure in pediatrics?

In this submission, the applicant requested a waiver of pediatric trials (b) (4) Division of Dermatology and Dental Products (DDDP) and Pediatric and Maternal Health Staff (PMHS) did not agree with the applicant's requested waiver for the following reason. Per the consult review from PMHS dated 12/3/2012, under PREA, a full waiver may be granted if

- Necessary trials are impossible or highly impracticable. This drug does not appear to apply to this criterion except for patients less than 2 years of age.
- There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups. This does not appear to be acceptable. Although concerns of HPA axis suppression exist, especially in younger pediatric patients, the applicant has not provided adequate documentation to suggest that desoximetasone spray would be unsafe in all pediatric age groups.
- The drug or biological product (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (II) is not likely to be used in a substantial number of pediatric patients. However, the applicant has not provided adequate justification to support that desoximetasone spray would not offer a meaningful health benefit to those pediatric patients with moderate to severe psoriasis.

DDDP recommends the applicant to conduct a safety trial to evaluate HPA axis suppression and the pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment in subjects age 2-16 years and 11 months with psoriasis. The trial should be conducted in sequential cohorts. A minimum of 30 evaluable subjects should be enrolled in each cohort:

Cohort 1: age 12 years to 16 years 11 months
Cohort 2: age 6 years -11 years and 11 months
Cohort 3: age 2 years to 5 years and 11 months

Approximately 2% of pediatric subjects with psoriasis are less than 2 years of age. Thus, the evaluation of pediatric subjects less than 2 years of age is waived.

This recommendation was agreed by the Pediatric Review Committee (PeRC) at the meeting on January 9, 2013.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (food, drugs, herbal products, smoking, alcohol use) influence the PK of Desoximetasone spray, 0.25%?

The effects of extrinsic factors on the PK of desoximetasone spray, 0.25% were not evaluated. Since this is a topical product, an effect of food is not anticipated.

2.5 General Biopharmaceutics

2.5.1 Is the to-be-marketed formulation identical to the one used in Phase 3 efficacy and safety trials?

The CMC Lead, Dr. Shulin Ding, confirmed that the 4 batches (L163-59328, L163-58859, L163-57868, L163-58221) used in the 8 clinical trials submitted in this NDA were the to-be-marketed formulation.

2.5.2 What is the final product composition?

Table 6 shows the components and composition of Desoximetasone spray, 0.25%.

Table 6: Quantitative Composition of Desoximetasone Spray, 0.25%

Strength (Label claim):	0.25% w/w	
Component and Quality Standard	**Quantity per unit** (mg/g)	**%** (w/w)
Desoximetasone, USP	2.5	0.25
Glyceryl Oleate, Taro	(b) (4)	(b) (4)
Isopropyl Alcohol, USP		23.4
Isopropyl Myristate, NF		(b) (4)
L-Menthol, USP		
Mineral Oil, USP		
Total Weight		**100%**

2.6 Analytical

2.6.1 What bioanalytical methods were used to assess drug concentrations?

Desoximetasone assay:

Desoximetasone concentrations in human plasma (containing K2-EDTA as anticoagulant) were assessed using liquid chromatography/tandem mass spectroscopy (LC-MS/MS). This method was used to analyze samples in trial DSXS-0805, and applicable for measuring concentrations of desoximetasone ranging from 50 to 1000 pg/mL.

Briefly, desoximetasone [redacted] (b) (4)

Cortisol assays:
HPA-axis function was measured based on cortisol response analyzed at local laboratories for each of the individual sites. Each local laboratory used a commercially available assay to quantitatively measure serum cortisol levels. A brief overview of the kits and procedures is provided below.

Table 7: The Local Laboratories Which Used Commercially Available Assay for Cortisol Levels

[redacted] (b) (4)

2.6.2 Were the bioanalytical methods adequately validated?

Desoximetasone assay:
The method for measuring desoximetasone in human plasma (containing K_2EDTA) by LC-MS/MS was adequately validated in the laboratories of [redacted] (b) (4) on behalf of Taro Pharmaceutical Industries Ltd. Desoximetasone is reported to be stable in plasma when stored at -20 ºC for up to 164 days. The duration from the first period of sample collection to the last day of sample analysis was 160 days and samples were stored at ≤-20 ºC during this time. The standard curve range was from 50-1000 pg/mL. Intra-day and Inter-day precision and accuracy was assessed at 4 quality control (QC) levels. Accuracy and precision at LLOQ was assessed using 6 replicates. A summary of precision and accuracy results is shown in Table 8.

Table 8: Precision and Accuracy Results of Desoximetasone Assay Validation

Standard Curve Range	50.0 – 1000.0 pg/mL (r^2=0.9906)
Lower Limit of Quantitation (LLOQ)	50.0 pg/mL
Average Recovery of Drug	94.57%
Intra-Day Accuracy	103.67-106.08%
Inter-Day Accuracy	105.06% (95% CI 92.17-117.94)
Intra-Day Precision Range	3.05 – 10.90%
Inter-Day Precision Range	5.25 – 9.20%

Cortisol assays:
For the commercial kit of [redacted], the electrochemiluminescence immunoassay "ECLIA" was used on the [redacted] immunoassay analyzer and validated by the manufacturer of [redacted] In-house validation was performed at [redacted] close to the same time frame of Trial DSXS 0805. The intra-assay precision range was between 1.7-3.8%, and the intra-day accuracy was 92.99-98.42%. The results were acceptable.

For the commercial kit of Vitros Cortisol Assay by Ortho-Clinical Diagnostics, it is performed using the Vitros Cortisol Reagent Pack and Vitros Immunodiagnostic Products Cortisol Calibrators on the Vitros ECi Immunodiagnostic System, and was validated by the manufacturer of [redacted]. In-house validation was performed at [redacted] close to the same time frame of Trial DSXS 0805. The quality control % difference was 3.8-10.1%. The results were acceptable.

For [redacted] developed acid protein precipitation assay, High Throughput Liquid Chromatography (HTLC) was used and the cortisol was detected by LC/MS/MS. This method was validated at [redacted] However, the applicant failed to submit the in-house quality control performed during a similar time frame as Trial DSXS 0805 after 3 information requests by the Agency. Therefore, the cortisol response test results of the 3 patients conducted in this laboratory were excluded from discussion and conclusion of HPA axis suppression in this review.

3 Detailed Labeling Recommendations

The following changes are recommended for section 5.1and 12 of the label. Additions are noted as double underline and deletions are noted as ~~strikethrough~~.

5.1 Effect on Endocrine System [redacted]

Topicort® [redacted] Topical Spray, [redacted] is a [redacted] topical corticosteroid that has been shown to suppress the HPA axis.

Systemic absorption of topical corticosteroids can produce reversible [redacted] (HPA) axis suppression with the potential for clinical

glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

In a (b) (4) including 21 subjects 18 years of age or older with moderate to severe plaque psoriasis, adrenal suppression was identified in 1 out of 12 in subjects having involvement of 10-15% of body surface area (BSA) and 2 out of 9 in subjects having involvement of >15% of BSA after treatment with Topicort Topical Spray twice a day for 28 days [see Clinical Pharmacology (12.2)]

Because of the potential for systemic absorption, use of topical corticosteroids may require that patients be periodically evaluated for HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent steroids, use over large surface areas, use over prolonged periods, use under occlusion, use on an altered skin barrier, and use in patients with liver failure.

An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, an attempt should be made to gradually withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation and protein regulation; however, the precise mechanism of action in psoriasis is unknown.

(b) (4)

12.2 Pharmacodynamics

Vasoconstrictor studies performed with Topicort Topical Spray in healthy subjects indicate that it is in the high to super-high range of potency as compared with other topical corticosteroids (b) (4)

(b) (4)

[redacted] (b) (4) were applied with Topicort Topical Spray twice a day for 28 days. Twenty-one subjects had evaluable serum cortisol levels and the proportion of subjects demonstrating HPA axis suppression was 8.3% (1 out of 12) in subjects having involvement of 10-15% of BSA, and 22.2% (2 out of 9) in subjects having involvement of > 15% of their BSA. In this trial HPA axis suppression was defined as serum cortisol level <18 mcg/dL 30-min post cosyntropin stimulation. In the 2 subjects returned for post-treatment follow-up, suppression reversed 28 days after the end of treatment.

12.3 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.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Plasma concentrations of desoximetasone were measured at two single random time points in [redacted] (b) (4) the HPA axis suppression trial [see Clinical Pharmacology (12.2)] in 24 subjects with psoriasis. The mean (% Coefficient of Variation) concentration of desoximetasone was 449 pg/mL (86%) at Day 14 and 678 pg/mL (135%) at Day 28. The concentration time profile following application of Topicort Topical Spray is not known [redacted] (b) (4)

4 Appendix

4.1 Individual Trial Reviews

4.1.1 Trial No. 10715005

Title: A Randomized, Evaluator Blinded, Within Subject, Single-Center Evaluation of the Vasoconstrictive Properties of Desoximetasone spray, 0.25% Compared to Seven Other Corticosteroids of Known Potency and a Placebo in Healthy Volunteers

Trial Initiation/Completion Dates:
4/19/08 (First subject dosed) to 4/20/08 (Last subject completed)

Objectives:
To determine the relative vasoconstrictive potency of a new desoximetasone spray, 0.25% formulation compared to a placebo spray (vehicle), and seven other marketed corticosteroid formulations of known potency.

Trial Centers: Single center in the U.S.

Design of Trial: Randomized, Evaluator Blinded, Within Subject, Single-Center, Phase I trial.

Trial Population Demographics: Thirty two healthy volunteers.
Age range: 18-47 years; **Race:** African American (62.5%), Caucasian (31.25%), other (6.25%); **Gender:** 3 Male (9.38%), 29 Female (90.63%); **Weight:** 106-186 lbs

Investigational Products:
Test Products:
Desoximetasone 0.25% Topical Spray [Lot # L163-57868]
Desoximetasone (placebo) 0% Spray [Lot # L163-58081]
Reference Products:
Clobex® (clobetasol propionate) 0.05% Spray [Lot # 47570]
Topicort® (desoximetasone) 0.25% Cream [Lot # H7062]
Flucinonide 0.05% Ointment [Lot # J7106]
Elocon® (mometasone furoate) 0.1% Ointment [Lot # 6-UHK-2]
Topicort® LP (desoximetasone) 0.05% Cream [Lot # 07076]
Cultivate® (fluticasone propionate) 0.05% Cream [Lot # Z150]
Hytone® (hydrocortisone) 2.5% Cream [Lot # JE0012]

Dosing Regimen, Mode of Administration and Treatment Duration:
The subjects were dosed on 4/19/08 and completed the trial approximately 18 hours after their first application of study drug. On day 1, an open washer was placed over each of the eleven sites and taped in place on its edges with hypoallergenic tape, so that the area to be treated was not occluded. Circular application sites were designated on the flexor surface of each forearm between the wrist and the elbow. The sites are 2 cm apart, center-to-center. Each subject was applied with 10 µl of each formulation to 9 sites on each

forearm. Two sites on each arm were left untreated. The formulations were applied to the designated sites according to a randomization schedule. Baseline ChromaMeter and visual assessments were started approximately 2 hours prior to first application. After dosing, the subjects were discharged until approximately 16 hours after application of the products when all subjects returned for product removal. The washers were detached and residual surface treatment was removed by gently wiping each site with a damp cotton ball that had been soaked in a weak, mild, room temperature hypo-allergenic soap solution. Each site was then wiped with a damp cotton ball that had been soaked in room temperature water to remove the soap solution. Lastly each site was wiped with one clean dry cotton ball. Visual scoring and ChromaMeter assessment were performed approximately 2 hours after product removal.

Pharmacodynamic(s): The degree of vasoconstriction was assessed using a single timepoint visual scoring as well as using a single timepoint ChromaMeter (a-scale reading) two hours after product removal. The sponsor's primary analysis was based on the ChromaMeter data while visual scoring data was collected for secondary purposes. The degree of skin blanching was visually evaluated at each site using a 4-point scale (0=no pallor; no change from surrounding area, 1=mild pallor; slight or indistinct outline of application site, 2=moderate pallor; discernible outline of application site, 3=intense pallor; clean, distinct outline of application site). Both the ChromaMeter operater measured and visual assessment evaluated the degree of blanching at each site predose and at approximately 18 hours after the application of the trial (approximately 2 hours after washing the test sites to remove study drug).

Analytical Methods: ChromaMeter Operator precision was evaluated from replicate evaluations (5 readings, at least 3 minutes apart) at 4 untreated skin sites on each arm of at least 4 different subjects. The within-site CV% for each operator was ≤10% and the overall mean difference as compared to a trainer was ≤10%.

Statistical Methods: The primary analysis was based on the ChromaMeter (a-scale) assessment data. The post-dose ChromaMeter readings were corrected for both the average pre-dose readings and the average readings from the untreated sites. The potency of the products was determined by the degree of blanching at 2 hours post-removal. All statistical tests were performed at a 5% (two-tailed) significance level. Within this analysis, pairwise comparisons of the mean assessment scores (ChromaMeter or visual) were performed using the Ryan-Einot-Gabril-Welsch Multiple Range Test (REGWQ) which controls the experiment wise Type 1 error rate at 5% under the complete null hypothesis. The null hypothesis states that the treatment vasoconstriction score means are equivalent. The relative potency of the test formulation of desoximetasone spray, 0.25% was estimated by comparing it with the reference products and placebo.

Results:
The potency rankings determined by primary analysis (ChromaMeter assessment) and secondary analysis (visual assessment) were as follows: Desoximetasone Spray, 0.25% was consistently shown to induce vasoconstriction similar to the 0.25% cream (Class 2 potency steroid). Clobetasol propionate, 0.05% spray (Class 1 potency steroid),

fluocinonide 0.05% ointment (Class 1 potency steroid identified by Sponsor, but Class 2 potency steroid according to the National Psoriasis Foundation), and mometasone furoate, 0.1% ointment (Class 2 potency steroid) also exhibited a similar degree of vasoconstriction. No statistically significant difference was observed between the untreated sites and the sites treated with the placebo spray, therefore demonstrating no significant pharmacologic activity. The applicant decided that Desoximetasone Spray, 0.25% was a super-high potency steroid. The potency rankings according to visual assessment results are shown in Table 9.

It is of note that there was a relative lack of discrimination between products and a low level of blanching observed in this trial for the high potency steroids relative to results in other trials. The applicant stated that this may be due to the high proportion of African Americans enrolled (20 subjects or 62.5%). It was also shown in this trial that there was a difference in vasoconstriction response between the African American and Caucasian populations in that lower ChromaMeter scores and higher visual scores were reported in the Caucasian population. This may be because results are more difficult to visualize or also due to decreased transcutaneous penetration in African Americans.

If restricting results to the 10 Caucasians, desoximetasone spray, 0.25% was similar to clobetasol propionate spray, 0.05% (as was the desoximetasone cream, 0.25%), in both ChromaMeter and visual assessment. The applicant concluded that desoximetasone spray, 0.25% is likely a Class 1 steroid.

Statistical Analysis:
In the ChromaMeter assessment result, the Ryan-Einot-Gabril-Welsch Multiple Range Test (REGWQ) for difference between Desoximetasone Spray 0.25% and Reference Products 1 to 5 (Class 1 to 4) was not statistically significant. The comparison between Reference Product (Class 7), Desoximetasone placebo, and untreated site was also not statistically different. In the visual assessment, the REGWQ test for difference between Desoximetasone Spray 0.25% and Reference Products 1 to 4 (Class 1 to 2) was not statistically significant. There was also no significant difference between Reference Product (Class 7), Desoximetasone placebo, and untreated site.
Based on the primary ChromaMeter data, the applicant considers Desoximetasone spray, 0.25% a Class I or Class II high potency steroid formulation relative to the seven other marketed corticosteroid formulations of known potency. There was no statistically significant difference between the placebo spray (Test 2) and the untreated site, therefore demonstrating no significant pharmacologic activity.

Safety:
There were no adverse events reported during this trial.

Reviewer's Comments on Trial No. 10715005

1. The applicant used both ChromaMeter assessment and visual assessment to evaluate the potency ranking; however, we typically rely on visual assessment for the reported values on visual blanching scoring. The fact that there is no statistically significant difference between Topicort® Spray, 0.25% and products

of Class 1 and 2 does not support the applicant's conclusion of classifying Topicort® Spray 0.25% as a super-high potency steroid.

2. It is noted that skin blanching response was less robust in African American subjects compared to Caucasian subjects. It is not clear if this was related to difficulty in assessing skin blanching in African American subjects or due to decreased percutaneous absorption. If restricting results to the 10 Caucasians, desoximetasone spray, 0.25% was similar to clobetasol propionate 0.025% spray (Class 1) and desoximetasone cream, 0.25% (Class 2) by visual assessment. Therefore, this result does not support that applicant's conclusion of classifying Topicort ® Spray 0.25% as a super-high potency steroid as well.

Conclusion on Trial No. 10715005

Desoximetasone spray, 0.25% should be classified as a Class 1/2 potency steroid, instead of a Class 1 super high potency steroid. This is based on the visual assessment result that Desoximetasone spray, 0.25% is comparable to four topical steroid products of Class 1 and Class 2 potency in its ability to cause vasoconstriction.

Table 9: Mean Visual Results in Order of Most to Least Potent

	Formulations	N	Mean (16 Hr Duration)	REGWQ Grouping*
Reference Product 3	Fluocinonide 0.05% Ointment, Taro Pharmaceuticals Inc., Lot No. J7106, Expiration Date 10/10 *(Class 2)*[a]	32	1.3125	A
Reference Product 2	Topicort® (desoximetasone) 0.25% Cream, Taro Pharmaceuticals Inc., Lot No. H7062, Expiration Date 08/10 *(Class 2)*	32	1.2969	A
Reference Product 4	Elocon® (mometasone furoate) 0.1% Ointment, Schering Corporation, Lot No. 6-UHK-2, Expiration Date 12/08 *(Class 2)*	32	1.1563	A
Test Product 1	Desoximetasone 0.25% Topical Spray, Taro Pharmaceuticals Inc., Lot No. L163-57868, Manufacture Date 09/06/07	32	1.1563	A
Reference Product 1	Clobex® (clobetasol propionate) 0.05% Spray, Manufactured by CPL, Marketed by Galderma Laboratories Inc., Lot No. 47570, Expiration Date 11/08 *(Class 1)*	32	1.1094	A
Reference Product 5	Topicort® LP (desoximetasone) 0.05% Cream, Taro Pharmaceuticals Inc., Lot No. 07076, Expiration Date 04/09 *(Class 3 or 4)*[b]	32	0.9375	B A
Reference Product 6	Cultivate® (fluticasone propionate) 0.05% Cream, Pharma Derm, a Division of Altana Inc., Lot No. Z150, Expiration Date 07/09 *(Class 5)*	32	0.6406	B
Test Product 2	Desoximetasone (placebo) 0.25% Spray, Taro Pharmaceuticals Inc., Lot No. L163-58081, Manufacture Date 01/16/08	32	0.2344	C
Reference Product 7	Hytone® (hydrocortisone) 2.5% Cream, Dermik Laboratories, a Division of Aventis Pharmaceuticals Inc., Lot No. JE0012, Expiration Date 03/09 *(Class 7)*	32	0.0156	C
Untreated Site	N/A	32	0.0000	C

*Products with the same Ryan-Einot-Gabriel-Welsh Multiple Range Test (REGWQ) grouping letter are not significantly different.

a. Fluocinonide 0.05% ointment is classified as a Class 1 by the applicant, but is classified as a Class 2 potency steroid according to both the National Psoriasis Foundation and the corticosteroid classification in "Corticosteroid classes: A quick reference guide including patch test substances and cross-reactivity, Jacob and Steele, J Am Acad Dermatol, April 2006; 723-727".

b. Topicort® LP (desoximetasone) 0.05% cream is classified as a Class 3 by the applicant, and is also classified as a Class 3 by the National Psoriasis Foundation. However, it is classified as a Class 4 according to the corticosteroid classification in "Corticosteroid classes: A quick reference guide including patch test substances and cross-reactivity, Jacob and Steele, J Am Acad Dermatol, April 2006; 723-727".

4.1.2 Trial No. DSXS 0805

Title: An Open Label, Safety/Efficacy Trial to Assess the Potential for Adrenal Suppression Following Multiple Dosing with Desoximetasone 0.25% Topical Spray in Patients with Moderate to Severe Plaque Psoriasis

Trial Initiation/Completion Dates: 2/23/2010 (first patient enrolled) to 6/22/2010 (last patient completed)

Objectives: The objective of this trial was to evaluate the potential of desoximetasone 0.25% topical spray to suppress HPA axis function. The secondary objectives were to evaluate the efficacy parameters and to evaluate the adverse event (AE) profile.

Trial Centers: Multicenter with three sites in the U.S.

Design of Trial: An Open Label, Safety/Efficacy Trial to Assess the Potential for Adrenal Suppression Following Multiple Dosing with Desoximetasone 0.25% Topical Spray in Patients with Moderate to Severe Plaque Psoriasis.

Trial Population Demographics: 12 patients in Group 1, and 12 patients in Group 2. **Age range:** Group 1: 18-74 years, Group 2: 21-73 years; **Race:** Group 1: 12 Caucasian (100%), Group 2: 2 African Americans (16.67%) and 10 Caucasian (83.33%); **Gender:** Group 1: 4 Female (33.33%) and 8 Male (66.67%), Group 2: 8 Female (66.67%) and 4 Male (33.33%); **Baseline Total BSA range:** Group 1: 1.65-2.36, Group 2: 1.73-2.45; **Baseline % BSA Affected:** Group 1: 10-12, Group 2: 16-40; **PGA:** Group 1: 3=Moderate: 8 patients (66.67%), 4=Severe: 4 patients (33.33%). Group 2: 3=Moderate: 3 patients (25%), 4=Severe (75%)

Investigational Product: Desoximetasone Spray 0.25% (Taro Pharmaceuticals, Inc.) Batch Number: L163-58859.

Dosing Regimen, Mode of Administration and Treatment Duration:
Twenty-four (24) patients 18 years of age or older with a confirmed diagnosis of moderate to severe plaque psoriasis with a Physicians Global Assessment (PGA) score of 3 (moderate) or 4 (severe) for the overall disease severity, 12 having involvement of 10-15% of their body surface area and 12 having involvement of > 15% of their body surface area were enrolled. Desoximetasone spray, 0.25% was applied gently and completely rubbed in to the affected areas twice a day (morning and evening) for 28 days. Patients were screened, including a cortisol response test, within 7 days prior to enrollment. Patients with normal adrenal function were assessed at Visit 2 and enrolled in the trial if eligible. They then returned to the clinic for assessment of signs and symptoms of psoriasis, adverse events, concomitant medications and compliance at Day 7, Day 14 and Day 28. Patients were required to give blood samples at baseline (Visit 1) and 2 post-treatment (Visit 4 and 5) for quantification of desoximetasone concentration in plasma. At Visit 5 (Day 28) patients underwent the final cortisol response test to assess HPA axis function after treatment with Desoximetasone.

HPA Axis Evaluation: Within 7 days prior to the first dose of study drug and at the end of the trial (Day 28 or early termination) all patients had a cortisol response test performed. Only those patients with normal adrenal function at baseline were enrolled and dispensed study drug. If at the end of the trial a patient had results from a cortisol response test that was suggestive of HPA axis suppression, they had follow up testing at least every 4 weeks until such time as the Investigator determined that adrenal function had returned to normal. The primary analysis was the proportion of patients in the trial with HPA axis suppression. The secondary analysis was a logistic regression of the proportion of patients in the trial with HPA axis suppression was performed with %BSA affected as a covariate.

Analytical Methods:
See Question-Based-Review Section 2.6.1.

Statistical Methods: Statistical significance was declared when the p-value was found to be less than or equal to 0.05. Statistical tests were two-tailed unless otherwise stated. Baseline comparability of the two groups was assessed using appropriate statistical tests (e.g., one-way analysis of variance, Fisher's exact test, Cochran-Mantel-Haenszel test). The groups were compared for basic demographics (age, gender, ethnicity and race), baseline total BSA, % BSA affected and baseline PGA.

Results:
The sponsor set the following criteria to be considered normal and showed no evidence of any abnormal HPA function or adrenal response in a cortisol response test:

- The basal (pre-Cortrosyn™ injection) cortisol concentration was ≥ 5 mcg/100mL
- Their 30 minute post-injection cortisol level was at least 7 mcg/100 mL greater than the basal level (≥ basal value +7)
- The post stimulation level was > 18 mcg/100 mL

The individual measurements by patient of cortisol response test result are listed in the table below:

Table 10: The individual measurements by patients of cortisol response test result

			Visit 1			Visit 5			Follow-Up		
Subject Number	Initials	Group	Basal	Post Inj.	Change from Basal	Basal	Post Inj.	Change from Basal	Basal	Post Inj.	Change from Basal
01-100	BEP	2	10.5	25.5	15.0	11.0	23.0	12.0			
01-101	PEP	2	15.1	31.0	15.9	10.3	28.6	18.3			
01-102	LBD	2	9.5	22.9	13.4	5.9	19.6	13.7			
01-103	JLM	2	15.2	27.0	11.8	8.7	20.1	11.4			
01-104	EAR	1	9.2	24.0	14.8	12.3	24.5	12.2			
01-105	GWT	1	7.4	25.0	17.6	6.1	21.9	15.8			
01-106	RHM	1	4.1	23.4	19.3	6.7	20.0	13.3			
01-107	RDP	1	12.2	25.5	13.3	9.3	25.0	15.7			
01-112	BJB	1	18.7	27.6	8.9	11.6	22.7	11.1			
02-202	OJE	2	15.0	22.8	7.8	8.3	21.9	13.6			
02-203	SVS*	2	12.1	32.2	20.1	4.2*	17.9*	13.7	9.8	23.5	13.70
02-207	ESC	2	7.6	26.3	18.7	7.0	22.2	15.2			
02-211	PRI*	2	11.2	20.3	9.1	6.4	17.9*	11.5	10.3	18.7	8.40
02-212	B-H*	1	10.6	18.5	7.9	5.3	17.9*	12.6			
02-213	BML	1	6.2	20.0	13.8	6.5	18.6	12.1			
02-217	R-L	1	11.9	25.9	14.0	11.9	24.4	12.5			
02-220	JNB	1	9.7	21.9	12.2	7.8	20.9	13.1			
02-222	PCH	1	17.6	24.9	7.3	6.8	18.8	12.0			
02-224	TMP	2	10.6	21.6	11.0	13.4	22.4	9.0			
02-225	PLS	1	12.4	25.0	12.6	10.4	22.8	12.4			
02-226	MDG*	1	9.5	23.9	14.4	4.6*	22.0	17.4	14.8	25.6	10.80
03-300	JLC	2	16.0	31.0	15.0	10.8	23.1	12.3			
03-301	MAH	2	13.9	26.3	12.4	14.8	27.9	13.1			
03-302	TGD*	2	13.8	26.6	12.8	1.2*	23.2	22.0			

*Abnormal results

* Three patients (Subject number 03-300, 03-301, and 03-302) from the third local laboratory (Quest) were removed from analysis and results in this review.

The concentrations of desoximetasone in the plasma samples from Visit 1 (Day -7) were below the level of detection for all patients. Samples were below the level of detection or unavailable for 4 enrolled patients for Visit 4 (Day 14) and for 3 enrolled patients for Visit 5 (Day 28). The mean (%CV) concentration of desoximetasone was 449 pg/mL (86%) at Day 14 and 678 pg/mL (135%) at Day 28. With the caveat that plasma desoximetasone concentrations were tested at baseline, Day 14, and Day 28 with unspecified time post dose, the applicant reported that there were no significant differences in the plasma drug levels of patients analyzed in either group, with or without HPA axis suppression.

Table 11: Plasma Desoximetasone Concentration Analysis

	N (%)	Mean pg/mL (Std Dev)	p-value
Visit 4			
Group 1 (10-15% BSA affected)	10	358.95 (180.49)	0.4276
Group 2 (> 15% BSA affected)	10	507.30 (540.12)	
Patients without HPA Axis Suppression Group 1	8	382.55 (196.72)	0.1337
Patients with HPA Axis Suppression Group 1	2	264.56 (1.70)	
Patients without HPA Axis Suppression Group 2	8	574.34 (548.42)	0.4652
Patients with HPA Axis Suppression Group 2	2	239.14 (234.47)	
Visit 5			
Group 1 (10-15% BSA affected)	10	350.01 (228.41)	0.1090
Group 2 (> 15% BSA affected)	12	951.12 (1176.34)	
Patients without HPA Axis Suppression Group 1	8	306.17 (202.92)	0.2461
Patients with HPA Axis Suppression Group 1	2	525.37 (323.16)	
Patients without HPA Axis Suppression Group 2	9	647.65 (503.24)	0.4444
Patients with HPA Axis Suppression Group 2	3	1861.51 (2222.64)	
Patients without HPA Axis Suppression Group 1 & 2	17	486.95 (418.94)	0.3431
Patients with HPA Axis Suppression Group 1 & 2	5	1327.06 (1741.19)	

* Sponsor's criteria were used to determine patients with or without HPA axis suppression in this table.

Table 12: Desoximetasone Plasma Concentrations after 14 and 28 Days of Application

Patient Group	Mean Blood Concentrations Excluding Patients with Values <LOQ[1,2]			Mean Blood Concentrations Including Patients with Values <LOQ[3]		
	N	Mean ± SD (pg/mL)	P-value	N	Mean ± SD (pg/mL)	P-value
Day 14						
Group 1 (10-15% BSA affected)	10[1]	358.95 ± 180.49	0.4276	11[4]	326.32 ± 202.56	0.4517
Group 2 (>15% BSA affected)	10[2]	507.30 ± 540.12		12	449.89 ± 511.55	
Day 28						
Group 1 (10-15% BSA affected)	10[2]	350.01 ± 228.41	0.1090	12	291.67 ± 247.48	0.0817
Group 2 (>15% BSA affected)	12	951.12 ± 1176.34		12	951.12 ± 1176.34	

Source: Sponsor Table 2.5:2
BSA=body surface area; LOQ=limit of quantitation
[1]Two patients omitted from analysis (one patient had a blood level of desoximetasone below the limit of quantitation and no sample was available for the other patient)
[2]Two patients omitted from analysis (both patients had a blood level of desoximetasone below the limit of quantitation)
[3]Values calculated independently from study report from data given in Sponsor Appendix 16.2.5
[4]One patient omitted from analysis, as no blood sample was obtained

Safety

9 patients (37.5%) reported a total of 14 adverse events during this trial. 5 patients (21%) had adrenal suppression, 1 patient (4%) had gastrointestinal disorders (vomiting), 1 patient (4%) had application site pruritus, 1 patient (4%) had sciatica, 1 patient (4%) had developed cyst, 1 patient (4%) had abnormal dreams, 1 patient (4%) had carpal tunnel syndrome, 2 patient(8%) had headaches, and 1 patient(4%) had hypertension.

Demographics:

Baseline Demographics			
		Treatment Groups	
		Group 1 N = 12	Group 2 N = 12
Age (years)	Mean ± SD	52.08 ± 15.01	46.75 ± 19.48
	Range	18-74	21-73
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18 – 40	2 (16.67%)	5 (41.67%)
	41 – 64	8 (66.67%)	3 (25.00%)
	65 – 75	2 (16.67%)	4 (33.33%)
	> 75	0 (0.00%)	0 (0.00%)
Gender	Female	4 (33.33%)	8 (66.67%)
	Male	8 (66.67%)	4 (33.33%)
Ethnicity	Hispanic or Latino	4 (33.33%)	2 (16.67%)
	Not Hispanic or Latino	8 (66.67%)	10 (83.33%)
Race	American Indian or Alaska Native	0 (0.00%)	0 (0.00%)
	Asian	0 (0.00%)	0 (0.00%)
	Black/African American	0 (0.00%)	2 (16.67%)
	Native Hawaiian or Other Pacific Islander	0 (0.00%)	0 (0.00%)
	White	12 (100.00%)	10 (83.33%)
	Other	0 (0.00%)	0 (0.00%)
Baseline Total BSA	Mean ± SD	2.00 ± 0.23	2.01 ± 0.22
	Range	1.65-2.36	1.73-2.45
Baseline %BSA Affected	Mean ± SD	10.50 ± 0.80	22.58 ± 9.68
	Range	10-12	16-40
PGA	3 = Moderate	8 (66.67%)	3 (25.00%)
	4 = Severe	4 (33.33%)	9 (75.00%)
	5 = Very severe	0 (0.00%)	0 (0.00%)

Analytical Method Validation:

Assay Method	Liquid chromatography/tandem mass spectroscopy (LC-MS/MS)
Analytical Site	Pharmalytics Ltd., Saskatoon, Saskatchewan, Canada
Compound	Desoximetasone (containing K_2EDTA)
Standard Curve Range	50.0 – 1000.0 pg/mL (r^2=0.9906)
Lower Limit of Quantitation (LLOQ)	50.0 pg/mL
Average Recovery of Drug	94.57%
Intra-Day Accuracy	103.67-106.08%
Inter-Day Accuracy	105.06% (95% CI 92.17-117.94)
Intra-Day Precision Range	3.05 – 10.90%
Inter-Day Precision Range	5.25 – 9.20%
Freeze-Thaw Stability	3 cycles
Bench-Top Stability	4 hours (20°C)
Processed Stability	48 hours (room temperature in mobile phase)
Long Term Stability	164 days (≤-20°C) *Sample analysis was conducted between 7/22/2010 and 8/2/2010, and the sample collection was between 2/23/2010 and 6/17-22/2010. The duration from the first sample collection to the last day of sample analysis was 160 days.*
Dissolution Integrity	Up to 4-fold
Recovery	93.43% (at 150 pg/mL), 96.41% (at 300 pg/mL), 93.88% (at 750 pg/mL)
Selectivity	No positive interference from endogenous plasma constituents at the retention times of the compounds of interest.
Reviewer's comments	***Method acceptable***

Cortisol assays:

In the original submission, there was no information on the manufacturer's assay procedures and validation results for each of the assay from 3 local laboratories. In the 74-day letter, the Agency requested the applicant to submit the above mentioned information, as well as data from in-house validations performed at each local laboratory. On 9/28/2012, the applicant has responded with incomplete information. The Agency therefore requested further information on in-house validations for the first 2 commercial kits (i.e., Cobas and Vitros) and method validation report and in-house validations and/or quality control results for the third local laboratory (b) (4). On 10/12/2012, the applicant responded with the information on the in-house validations of the first 2 commercial kits, but incomplete information on the third local laboratory. The Agency sent out the final information request on 11/20/2012. However, the applicant's response on 11/26/2012 still lacked the information on the in-house quality control results during the similar time frame of the trial conducted in the third local laboratory.

For the commercial kit of Cobas Elecsys Cortisol Assay by [redacted], it is an approved kit with 510(k) number of K070788 by Center for Devices and Radiological Health (CDRH). In-house validation was performed at [redacted] close to the same time frame of Trial DSXS 0805. The intra-assay precision range was between 1.7-3.8%, and the intra-day accuracy was 92.99-98.42%. The results were acceptable.

For the commercial kit of Vitros Cortisol Assay [redacted], it is an approved kit with 510(k) number of K070788 by CDRH. In-house validation was performed at [redacted] close to the same time frame of Trial DSXS 0805. The quality control % difference was 3.8-10.1%. The results were acceptable.

For Quest developed acid protein precipitation assay, this method was validated at [redacted] This is not an approved kit by CDRH. The validation conducted by [redacted] in 2002 was acceptable. However, the applicant failed to submit the in-house quality control results performed during the same time frame of Trial DSXS 0805 after 3 information requests. Therefore, the cortisol response test results of the 3 patients (Subject number 03-300, 03-301, and 03-302) conducted in this laboratory were excluded from discussion and conclusion of HPA axis suppression in this review.

Reviewer's comments on Trial No. DSXS 0805:
The sponsor's criteria are different from the single criterion of response to cosyntropin stimulation of >18 µg/dL 30 minutes after stimulation recommended by the Agency. Depending on which criteria is utilized, the results of HPA suppression would be different.

If using the sponsor's criteria, a total of 4 out of 21 patients or 19% had a serum cortisol concentration at Day 28 that met at least one of the criteria for adrenal suppression. Among the 4 patients, 2 out of 12 patients (17%) are in the group with 10-15% BSA affected and 2 out of 9 patients (22%) are in the group with >15% BSA affected.

If using the FDA's single criterion, 3 out of 21 patients or 14% met the criterion for adrenal suppression. Among the 3 patients, 1 out of 12 patient (8%) is in the group with 10-15% BSA affected and 2 out of 9 patients (22%) are in the group with >15% BSA affected. This FDA's single criterion is used to evaluate the HPA axis function in patients receiving desoximetasone spray in the review of this submission.

The patient (Subject Number 02-226) who met the sponsor's but not the FDA's criteria for adrenal suppression had a basal cortisol concentration of 4.6 mcg/100mL on Day 28, but increased to 22 mcg/100mL post-injection. In a paper published by McGill, et al. (P.E. McGill, W.R. Greig, M.C.K. Browning, J.A. Boyle. Plasma cortisol response to synacthen (β^{1-24} CIBA) at different times of the day in patients with rheumatic diseases. Ann Rheum Dis. 1967;26:123-125), the result showed that in each subject the basal plasma cortisol levels (before Synacthen administration) fell during the day time, which indicates normal diurnal rhythm. On the other hand, the plasma cortisol levels after

Synacthen stimulation were the same throughout the day. Therefore, the authors concluded that only the criterion of the plasma cortisol level attained 30 minutes after Synacthen injection should be used.

Regarding desoximetasone plasma concentrations, 3 PK samplings were collected in all subjects, one at baseline and one on each Day 14 and Day 28, at least 8 hours after dosing. It appears that plasma desoximetasone concentrations are higher in the subjects with HPA axis suppression by sponsor's criteria on Day 28 as compared to other subjects, although it is not statistically significant. However, there were only single PK samplings on Day 14 and 28, and the full PK profile following application of desoximetasone spray, 0.25% was not evaluated and is not known. Therefore, without full PK profile, we cannot rely on the single randomly timed plasma drug levels to correlate with patients with or without HPA axis suppression.

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

/s/

AN-CHI LU
01/18/2013

DOANH C TRAN
01/18/2013

EDWARD D BASHAW
01/18/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 204141 **Applicant: Taro Pharmaceuticals USA, Inc.** **Stamp Date: 6/12/2012**

Drug Name: Topicort (desoximetasone) spray, 0.25% **NDA/BLA Type: Original**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?		X		
Criteria for Assessing Quality of an NDA					
	Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	X			Cortisol concentrations are in section 5.3.4.1.23. Desoximetasone concentrations are in section 5.3.4.1.25.3.1.
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X			
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?		X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Sponsor requested waiver of pediatric studies.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			

	General				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
17	Was the translation from another language important or needed for publication?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

See comments for sponsor at end of filing memorandum.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**204141**	**Brand Name**	**Topicort**
OCP Division	**Division of Clinical Pharmacology 3**	**Generic Name**	**Desoximetasone**
Medical Division	**Division of Dermatology and Dental Product**	**Drug Class**	**Topical corticosteroid**
OCP Primary Reviewer	**Doanh Tran, R.Ph., Ph.D**	**Indication(s)**	**Relief of (b) (4) psoriasis in patients 18 years of age or older**
OCP Secondary Reviewer	**Capt. E. Dennis Bashaw, Pharm. D.**	**Dosage Form**	**Topical spray**
		Dosing Regimen	**Apply a thin film to the affected skin areas twice daily. Rub in gently.**
Date of Submission	**6/12/2012**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review	**1/21/2013**	**Sponsor**	**Taro Pharmaceuticals USA, Inc.**
PDUFA Due Date	**4/12/2013**	**Priority Classification**	**Standard**
Division Due Date	**1/21/2013**		

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) -				
Healthy Volunteers-				
single dose:	x	1		Vasoconstriction study 10715005
multiple dose:				
Patients-				
single dose:				
multiple dose:	x	1		HPA/PK study DSXS 0805
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:	x	1		Dose ranging study DSXS 0906
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	2		Phase 3 trials DSXS 0808 and DSXS 0914
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		5		

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**x**	
Comments sent to firm?	**x**	Comments at end of filing memo will be sent to the sponsor in Day 74 letter.
QBR questions (key issues to be considered)	• **Rate of HPA suppression** • **Systemic exposure to desoximetasone** • **Potency classification based on vasoconstrictor assay**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memorandum

Clinical Pharmacology Review

NDA: 204141
Compound: Desoximetasone spray, 0.25%
Sponsor: Taro Pharmaceuticals USA, Inc.

Date: 7/10/2012
Reviewer: Doanh Tran

Background: Taro is submitting this New Drug Application (NDA) for Desoximetasone Spray, 0.25% under Section 505(b)(1) of the Federal Food, Drug, and Cosmetics (FD&C) Act. Desoximetasone Spray, 0.25% represents a new non-aqueous spray formulation. It is delivered with a spray pump, with each (b) (4) spray delivering 0.294 mg of desoximetasone, USP.

Desoximetasone Spray, 0.25% is proposed for the treatment of (b) (4) in patients 18 years of age and older. The proposed dosing and administration instructions are the same as approved for Topicort® Cream and Ointment, 0.25%. The proposed dosage is to apply a thin film to the affected skin areas twice daily.

Clinical development program:
Taro has sponsored a total of eight clinical trials conducted in support of the development of Desoximetasone Spray, 0.25%. One trial was performed in subjects with moderate to severe plaque psoriasis to measure HPA axis suppression induced by Desoximetasone Spray, 0.25% with limited pharmacokinetic (PK) sampling in a subset. Four Phase 1 trials were performed in healthy volunteers, evaluating vasoconstriction, phototoxicity, photoallergy, and cumulative irritation and sensitization potential of Desoximetasone Spray, 0.25%. The remaining three trials were a Phase 2 dose comparison study that included a lower dose spray, Desoximetasone Spray, 0.05%, and two Phase 3 trials in which the efficacy of Desoximetasone Spray, 0.25% was evaluated in patients with moderate to severe plaque psoriasis.

<u>HPA axis suppression trial DSXS-0805:</u>
Trial DSXS-0805 was an open-label trial to assess the potential for HPA axis suppression following multiple doses of Desoximetasone Spray, 0.25% in 24 patients with moderate to severe plaque psoriasis.

Briefly, at baseline and following 28 days of twice daily use of Desoximetasone Spray, 0.25%, patients underwent cortisol response testing. A patient was considered to have normally functioning HPA axis if he/she had a basal serum cortisol concentration >5 µg/100 mL and a response to cosyntropin stimulation of 18 µg/dL or higher 30 minutes after stimulation (representing an increase of at least 7 µg/dL above the basal concentration). These criteria are different than the single criterion of response to

(b) (4)

cosyntropin stimulation of 18 μg/dL or higher 30 minutes after stimulation recommended by FDA. The results for HPA suppression is dependent on whether the sponsor's or the FDA's criteria are used and are noted below.

Overall, 5 patients or 21% (3 patients if using FDA's criteria) had a serum cortisol concentration at Day 28 that met at least one of the criteria for adrenal suppression, 2 (1 if using FDA's criterion) patients in the group with 10-15% BSA affected (16.7%) and 3 (2 if using FDA's criterion) patients in the group with >15% BSA affected (25.0%), a difference that is not statistically significant. In the 3 patients with post-treatment follow-up, suppression reversed 28 days after the end of treatment (the other 2 patients did not return for follow-up).

In trial DSXS-0805, 3 PK samplings were also obtained in all subjects, one at baseline and one on each Day 14 and Day 28, at least 8 hours after dosing. A summary of results are shown in Table 1. Plasma desoximetasone concentrations appear to be higher in the subjects with HPA axis suppression as compared to other subjects (grouped by BSA affected by psoriasis). However, it should be noted that there were only single PK samplings on Days 14 and 28 and the full PK profile following application of desoximetasone spray, 0.25% was not evaluated and is not known.

Table 1: Summary of desoximetasone concentration (Study DSXS-0805)

Patient Group	Mean Blood Concentrations Excluding Patients with Values <LOQ[1,2]			Mean Blood Concentrations Including Patients with Values <LOQ[3]		
	N	Mean ± SD (pg/mL)	P-value	N	Mean ± SD (pg/mL)	P-value
Day 14						
Group 1 (10-15% BSA affected)	10[1]	358.95 ± 180.49	0.4276	11[4]	326.32 ± 202.56	0.4517
Group 2 (>15% BSA affected)	10[2]	507.30 ± 540.12		12	449.89 ± 511.55	
Day 28						
Group 1 (10-15% BSA affected)	10[2]	350.01 ± 228.41	0.1090	12	291.67 ± 247.48	0.0817
Group 2 (>15% BSA affected)	12	951.12 ± 1176.34		12	951.12 ± 1176.34	

Source: Sponsor Table 2.5:2
BSA=body surface area; LOQ=limit of quantitation
[1]Two patients omitted from analysis (one patient had a blood level of desoximetasone below the limit of quantitation and no sample was available for the other patient)
[2]Two patients omitted from analysis (both patients had a blood level of desoximetasone below the limit of quantitation)
[3]Values calculated independently from study report from data given in Appendix 16.2.5
[4]One patient omitted from analysis, as no blood sample was obtained

Vasoconstriction trial 10715005:

The data suggest that skin blanching of desoximetasone spray 0.25% was similar to products of Class 1 and Class 2 (the was no statistically significant separation in response to reference products of Class 1 and Class 2 in this study). Skin blanching response was less robust in African American subjects compared to Caucasian subjects. It is not clear if

this was related to difficulty in assessing skin blanching in African American subjects or due to decreased percutaneous absorption.

Phase 2 dose-finding trial DSXS-0906:
Study DSXS-0906 evaluated two dosing regimens (once or twice a day) of two strengths of Desoximetasone Spray (0.05% and 0.25%). On the basis of efficacy findings in this trial, the 0.25% strength, applied twice daily, was chosen for the Phase 3 randomized, vehicle-controlled trials (DSXS-0808 and DSXS-0914).

Special population:
Pediatric: The sponsor requested a waiver of pediatric studies citing low prevalence of psoriasis in pediatrics, safety risk of potent corticosteroids, and available alternatives for treatment of psoriasis.

Clinical vs. to-be-marketed formulation:
The CMC Lead, Dr. Shulin Ding, confirmed that the 4 batches (L163-59328, L163-58859, L163-57868, L163-58221) used in the 8 clinical trials submitted in this NDA were the to-be-marketed formulation.

Method validation:
Desoximetasone assay:
A method for measuring desoximetasone in human plasma (containing (b) (4)) by liquid chromatography/tandem mass spectroscopy (LC-MS/MS) was developed and validated in the laboratories of (b) (4) on behalf of Taro Pharmaceutical Industries Ltd. This method was used to analyze samples in trial DSXS-0805. Desoximetasone is reported to be stable in plasma when stored at -20 ºC for up to 164 days. The duration from the first period of sample collection to the last day of sample analysis was 160 days and samples were stored at ≤-20 ºC during this time. The method validation report and bioanalysis report for Study DSXS-0805 are available for review.

Cortisol assays:
HPA-axis function was measured based on cortisol response analyzed at local laboratories for each of the individual sites. Each local laboratory used a commercially available assay to quantitatively measure serum cortisol levels. A brief overview of the kits and procedures is provided below.

No in-house validation results were provided to support analysis at each clinical site.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 204141 is fileable.

Comments for sponsor:
In trial DSXS-0805, serum cortisol concentrations were analyzed at local laboratories using 3 different commercial kits. Submit the manufacturer's assay procedures and validation results for each kit. In addition, provide data from in-house validations performed at each local laboratory confirming that the kits were performing as expected at the local laboratories used in trial DSXS-0805.

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/s/

DOANH C TRAN
07/24/2012

EDWARD D BASHAW
07/25/2012