CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204141Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204141
Priority or Standard	Standard
Submit Date(s)	June 11, 2012
Received Date(s)	June 12, 2012
PDUFA Goal Date	April 12, 2013
Division / Office	DDDP/ ODE III
Reviewer Name(s)	Melinda McCord, M.D.
Review Completion Date	January 30, 2013
Established Name	Desoximetsone
(Proposed) Trade Name	Pending
Therapeutic Class	Topical corticosteroid
Applicant	Taro Pharmaceuticals, Inc.
Formulation(s)	Topical spray
Dosing Regimen	Twice per day
Proposed Indication(s)	The relief of (b) (4) plaque psoriasis in patients 18 years of age or older
Intended Population(s)	18 years of age or older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends an approval action for this new drug application regarding TRADENAME (desoximetasone) Topical Spray, 0.25% for the treatment of plaque psoriasis of the body in patients 18 years and older.

Labeling negotiations are still in progress and review of the proposed Proprietary Name by the Office of Surveillance and Epidemiology (OSE) is pending as of the date of this clinical review. This recommendation is contingent upon the successful completion of negotiations with the applicant regarding labeling and final recommendation from the Office of Compliance regarding the facilities inspections.

1.2 Risk Benefit Assessment

Desoximetasone topical spray, 0.25% is a corticosteroid indicated for the treatment of plaque psoriasis of the body in patients 18 years and older.

The applicant conducted 2 multicenter, randomized, double-blind, vehicle- controlled clinical trials (DSXS-0808 and DSXS-0914) enrolling a total of 240 subjects aged 18 years and older with moderate to severe plaque psoriasis of the body. In both trials, subjects applied desoximetasone topical spray or vehicle spray (randomized 1:1) to the affected areas twice daily for 4 weeks. Enrolled subjects had a minimum body surface area of involvement of 10%, a Physician's Global Assessment score (PGA) of 3 (moderate) or 4 (severe), and a target lesion with a plaque elevation score of at least 3 and total lesion severity score (TLSS) of at least 7. Subjects were evaluated using a 6-category PGA scale and a 6-category TLSS scale ranging from 0 (clear) to 5 (very severe).

Efficacy was assessed at Week 4 as the proportion of subjects who were considered a Clinical Success ("clear" or "almost clear" according to the PGA scale) AND a Treatment Success for the Target Lesion ("clear" or "almost clear" for each of the three signs of erythema, scaling and plaque elevation). Desoximetasone topical spray, 0.25% was statistically superior to vehicle spray for the treatment of plaque psoriasis of the body in both Phase 3 trials.

In trial DSXS-0808, 30.5% of subjects achieved Clinical Success and 39.0% achieved Treatment Success in the desoximetasone topical spray group while 5.0 % of subjects achieved Clinical Success and 6.7% achieved Treatment Success in the vehicle spray group. In trial DSXS-0914, 53.3% of subjects achieved Clinical Success and 53.3%

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achieved Treatment Success in the desoximetasone topical spray group while 18.3 % of subjects achieved Clinical Success and 16.7% achieved Treatment Success in the vehicle spray group.

The applicant submitted safety data from eight clinical trials in the marketing application for desoximetasone topical spray. This reviewer evaluated safety data from two Phase 3 trials (DSXS-0808 and DSXS-0914) enrolling 240 subjects, a dose range finding Phase 2 trial (DSXS-0906) enrolling 151 subjects, a vasoconstriction trial enrolling 32 subjects (10715005), an HPA axis suppression trial (DSXS-0805) enrolling 24 subjects, a phototoxicity trial (DSXS-0904) enrolling 38 subjects, a photoallergenicity trial enrolling 58 subjects and an irritation/sensitization trial enrolling 297 subjects.

The primary safety evaluation was conducted with data collected from all subjects who participated in the 3 multicenter, vehicle- controlled trials (DSXS-0808, DSXS-0914 and DSXS-0906) and were exposed to desoximetasone topical spray or vehicle spray applied twice per day for 28 days. The safety population consisted of a total of 284 subjects age 18 years and above with moderate to severe plaque psoriasis. A total of 149 subjects applied desoximetasone topical spray 0.25% twice per day and 135 subjects applied vehicle spray twice per day.

There were no deaths or non-fatal serious adverse events (SAEs) among subjects in the development program. Three subjects (1%) in the safety population reported adverse events assessed as severe in intensity. Review of the Case Report Forms indicated that these severe AEs were related to the study product. In the desoximetasone topical spray treatment group, one subject reported severe pruritus at the application site and one subject reported ulceration. In the vehicle spray treatment group, one subject reported severe redness on her legs at the application site.

The incidence of adverse events in the safety population resulting in subject discontinuation was 0.8% in the desoximetasone topical spray treatment group and 3.0% in the vehicle spray treatment group. One subject in the desoximetasone topical spray group reported application site pruritus and psoriasis which led to discontinuation from the trial. Four subjects in the vehicle spray group reported the following adverse events which led to discontinuation from the trial: application site burning, application site dryness and itching, application site erythema, and application site stinging and worsening of psoriasis.

Among the subjects in the safety population, at least one adverse event (AE) was reported by 20% of subjects in the desoximetasone topical spray treatment group and 28% of subjects in the vehicle spray treatment group. The most common adverse reactions (≥1%) in subjects exposed to desoximetasone topical spray included: application site dryness (2.7%), application site irritation (2.7%), and application site pruritus (2.0%). However, the incidence of these reactions was greater in the vehicle spray group than the desoximetasone topical spray group.

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The applicant conducted trial DSXS-0805 in adult subjects with a diagnosis of moderate to severe plaque psoriasis to provide data regarding systemic exposure and effect of desoximetasone topical spray 0.25% on the hypothalamic-pituitary axis. Twenty-one subjects had evaluable serum cortisol levels. The proportion of subjects demonstrating HPA axis suppression was 8.3% (1/12) in subjects with involvement of 10-15% of BSA, and 22.2% (2 / 9) in subjects with involvement of > 15% of their BSA. HPA axis suppression was defined as serum cortisol level ≤18 mcg/dL 30-min post cosyntropin stimulation.

In conclusion, based on the data from eight clinical trials in the NDA submission, the applicant established the safety and efficacy of desoximetasone topical spray for the treatment of plaque psoriasis of the body in patients aged 18 years and older.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) or additional risk management activities to augment safety information contained in product labeling are not recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

Clinical Post-Marketing Requirements

The applicant submitted data from eight clinical trials enrolling subjects 18 years and older in the marketing application for desoximetasone topical spray. Based on the lack of pediatric HPA axis suppression data with desoximetasone, and the risk/benefit profile of alternative therapies, the Agency requires that the applicant conduct following trial under PREA:

> Conduct a trial in 100 evaluable pediatric patients with psoriasis of the body ages 2 to 16 years and 11 months. Evaluate the safety and effect of desoximetasone topical spray, 0.25% on the hypothalamic-pituitary axis and pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment. Conduct the trial in sequential cohorts
>
> Cohort 1: age 12 years to 16 years 11 months
> Cohort 2: age 6 years -11 years and 11 month
> Cohort 3: age 2 years to 5 years and 11 months
>
> Final Protocol Submission: 4/30/2014
> Trial Completion: 4/30/2016
> Final Report Submission: 4/30/2017

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We are deferring submission of the pediatric trial required under PREA for ages 2 to 16 years and 11 months for this application because this product is ready for approval for use in adults and the pediatric trial has not been completed.

Non-Clinical Post-Marketing Requirements

Conduct a two year dermal rat carcinogenicity study.

Final Protocol Submission: 4/30/2015
Trial Completion: 5/31/2017
Final Report Submission: 5/31/2018

We are deferring submission of the long-term carcinogenicity data based on:
1) the historical use of desoximetasone cream 0.25%, gel 0.25% and ointment 0.25% has provided no known signals suggestive of carcinogenic potential and
2) desoximetasone was negative in a standard battery of genetic toxicology studies.

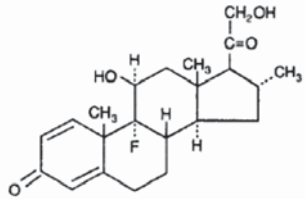
2 Introduction and Regulatory Background

On June 11, 2012, Taro Pharmaceuticals Inc. submitted a 505 (b)(1) New Drug Application (NDA) seeking approval to market desoximetasone topical spray, 0.25%.

2.1 Product Information

TRADENAME (desoximetasone) Topical Spray, 0.25% contains desoximetasone as the active ingredient.

Desoximetasone is a corticosteroid with the chemical name of pregna-1, 4-diene-3, 20-dione, 9-fluoro-11, 21-dihydroxy-16-methyl-, (11ß,16α). Desoximetasone has the molecular formula of $C_{22}H_{29}FO_4$ and a molecular weight of 376.47. The structural formula is:



Source: Proposed labeling NDA 20-4141

Each gram of TRADENAME (desoximetasone) Topical Spray, 0.25% contains 2.5 mg of desoximetasone in a clear, colorless liquid with the following inactive ingredients: glyceryl oleate, isopropyl alcohol (23.4%), isopropyl myristate, L-menthol, and mineral oil. Topicort Topical Spray is co-packaged with a manual spray pump for installation by the pharmacist prior to dispensing to patients.

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Each [redacted] (b) (4) spray delivers [redacted] (b) (4) of desoximetasone.
See Section 9.2 of this review.

Review of Proprietary Name:

In a letter dated November 7, 2012, the applicant submitted a Request for Proprietary Name Review for desoximetasone spray, 0.25%. Taro selected the proprietary name "Topicort" as it is the current name used for their other approved desoximetasone formulations.

In compliance with the standardized form of nomenclature in USP<1121>, the established name proposed for the drug product is "Topicort (desoximetasone) Topical Spray." As the dosage form "spray" may have multiple routes of administration (e.g. nasal, oral and topical), the route of administration is included in the established name to ensure the safe use of the drug product.

2.2 Tables of Currently Available Treatments for Proposed Indication(s)

Topical corticosteroids which were first introduced in the early 1950s are a mainstay of treatment for plaque psoriasis. Corticosteroids exhibit anti-inflammatory, immunosuppressive and anti-proliferative properties and are available as prescription products and over-the- counter low potency products. FDA approved products for the topical treatment of psoriasis include: topical corticosteroids, vitamin D analogs and retinoids. Examples of FDA approved products are presented below.

Table 1: FDA Approved Products for the Topical Treatment of Psoriasis

Product Name	Applicant	NDA #	Approval Date	Indication/ Age in Labeling
Taclonex (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Topical Suspension	Leo Pharma	022185 S-10	10/ (b) (4) /2012	topical treatment of plaque psoriasis of the scalp and body in patients 18 years of age and older
Sorilux (calcipotriene) Foam 0.005%	Stiefel	NDA 22563 S-2	9/27/2012	topical treatment of plaque psoriasis of the scalp and body in patients 18 years of age and older
Vectical	Galderma	022087	1/23/2009	topical treatment of mild to

(calcitriol) Ointment	Laboratories			moderate plaque psoriasis in adults 18 years and older.
Taclonex (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Ointment	Leo Pharma	021852	1/9/2006	topical treatment of psoriasis vulgaris in adults 18 years of age and older
Clobex (clobetasol propionate) 0.05% Spray	Galderma Laboratories	021835	10/27/2005	topical treatment of moderate to severe plaque psoriasis affecting up to 20% body surface area (BSA) in patients 18 years of age or older
Clobex (clobetasol propionate) shampoo, 0.05%	Galderma Laboratories	021644	3/25/2004	treatment of moderate to severe forms of scalp psoriasis in subjects 18 years of age and older
Tazorac (tazarotene) Cream 0.05%, 0.1%	Allergan	021184	9/29/2000	topical treatment of patients with plaque psoriasis. ≥18 years *
Tazorac (tazarotene) Gel 0.05%, 0.1%	Allergan	020600	6/13/1997	topical treatment of patients with stable plaque psoriasis of up to 20% body surface area involvement. ≥12 years **
Dovonex (calcipotriene) Cream 0.005%	Leo Pharma	020554	7/22/1996	treatment of plaque psoriasis ≥18 years ***

Source: Adapted from Table 1 from NDA 22-563
*The safety and efficacy of tazarotene cream have not been established in patients with psoriasis under the age of 18 years (Current labeling: Pediatric Use Section)
**The safety and efficacy of tazarotene gel have not been established in pediatric patients under the age of 12 years. (Current labeling: Pediatric Use Section)
***Safety and effectiveness (of Dovonex Cream 0.005%) in pediatric patients have not been specifically established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk than adults of systemic adverse effects when they are treated with topical medication. (Current labeling: Pediatric Use Section)

2.3 Availability of Proposed Active Ingredient in the United States

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Desoximetasone is marketed in three formulations (cream, gel and ointment) and two concentrations (0.25% and 0.05%) as summarized in Table 2. Taro acquired the Topicort brand in 2003 and markets all products as generics except Topicort® 0.05% Ointment. All of the marketed formulations of desoximetasone were evaluated in subjects with psoriasis and atopic dermatitis and were approved for the "relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses."

Table 2: Availability of Proposed Active Ingredient in the United States

Generic Name and Formulation	Brand Name	Applicant/	NDA/ANDA Number	FDA Approval Date
Desoximetasone cream* 0.25%	Topicort®	Taro Pharmaceuticals Inc	NDA 017856	2/28/1977
Desoximetasone cream* 0.05%	Topicort® LP	Taro Pharmaceuticals Inc	NDA 018309	3/28/1980
Desoximetasone gel* 0.05%	Topicort®	Taro Pharmaceuticals Inc	NDA 018586	3/29/82
Desoximetasone ointment* 0.25%	Topicort®	Taro Pharmaceuticals Inc	NDA 018763	10/3/1983
Desoximetasone ointment 0.05%	Topicort®	Taro Pharmaceuticals Inc	NDA 018594	1/17/1985
Desoximetasone cream 0.25%	Topicort®	Taro Pharmaceuticals Inc	ANDA 073193	11/29/1990
Desoximetasone cream 0.05%	Topicort®	Taro Pharmaceuticals Inc	ANDA 073210	11/30/1990
Desoximetasone Ointment 0.25%	Topicort®	Taro Pharmaceuticals Inc	ANDA074286	6/7/1996
Desoximetasone gel 0.05%	Topicort®	Taro Pharmaceuticals Inc	ANDA 074904	7/14/1998

Source: Drugs@FDA
***Marketing status: discontinued**
****There are other manufacturers of generic desoximetasone products.**

2.4 Important Safety Issues With Consideration to Related Drugs

Topical corticosteroids constitute a class of primarily synthetic steroids which are used as anti-inflammatory and anti-pruritic agents. Adverse reactions associated with desoximetasone and other members of the corticosteroid pharmacologic class are well characterized.

Per current labeling of topical desoximetasone products (Precautions Section), adverse reactions resulting from systemic absorption of topical corticosteroids include: hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, hyperglycemia and unmasking of latent diabetes. 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, use in patients with liver failure and use of more than one corticosteroid-containing product at the same time.

Per current labeling of topical desoximetasone products (Precautions Section), local adverse reactions may include: atrophy, striae, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions. Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Some local reactions may not be reversible.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio (Pediatric Use section of current labeling of Topicort (desoximetasone) ointment, cream and gel.) Adverse reactions observed in pediatric patients exposed to topical corticosteroids include: Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients.

Corticosteroids including desoximetasone are Pregnancy Category C products. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration at doses 3 to 30 times the human dose of TRADENAME (desoximetasone) Topical Spray, 0.25% based on a body surface area comparison. There are no adequate and well-controlled studies in pregnant women. (Section 8.1 Pregnancy of labeling).

Refer to Section 9.1 of this review for recommendations regarding labeling.

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2.5 Summary of Presubmission Regulatory Activity Related to Submission

The applicant submitted IND 101789 for desoximetasone topical spray, 0.25% on February 27, 2008. The applicant did not request or attend a Pre-IND Meeting or End of Phase 2 Meeting; the applicant did not request a special protocol assessment.

The Agency held a Pre-NDA Meeting with the applicant on July 20, 2011 to discuss the content and format of the proposed New Drug Application (NDA) submission for desoximetasone topical spray. The Agency stated that the indication for desoximetasone topical spray, 0.25% would be based upon the population studied in the Phase 3 trials. As the two clinical trials (DSXS-0808 and DSXS-0914) enrolled only subjects with moderate to severe psoriasis, these trials were not sufficient to support the proposed indication of (b) (4)

2.6 Other Relevant Background Information

The Agency provided comments regarding protocol submissions in the following correspondences:

- 07/06/2009: Advice letter regarding Phase 1/Phase 2/Phase 3 protocols
- 11/04/2009: Advice letter regarding Phase 2 protocol
- 01/21/2010: Advice letter regarding Phase 1/Phase 2 protocols

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission is adequate. The Division requested that the Office of Scientific Investigations (OSI) conduct clinical inspections of 2 domestic sites chosen for the inconsistent results in the co-primary endpoints (clinical success and treatment success of the target lesion.) After completion of the site inspections, the final classification of the two sites was “NAI” (No deviation from regulations).

Table 3: Clinical Site Inspections

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
David H. Horowitz, M.D. Dermatology Research Associates 1900 Patterson Street, Suite 104 Nashville, TN 37203	DSXS 0808/ Site #6/ 19 subjects	10-11 Sep 2012	NAI
Christopher A. Moeller, M.D. Compliant Clinical Research of Wichita, Inc. 250 North Rock Road, Suite 340 Wichita, KS 67206	DSXS 0808/ Site #1/ 12 subjects	5-6 Sep 2012	NAI

The reviewer for the Office of Scientific Investigations, Roy Blay, Ph.D., concluded: (Review dated 12/26/2012):

> "The data generated by these clinical sites and submitted by the sponsor appear adequate in support of the respective indication."

3.2 Compliance with Good Clinical Practices

The applicant certifies that the trials in their development program were conducted In compliance with the requirements of the Code of Federal Regulations (21 CFR), Parts 50, 54, 56, 312, and 314, and the International Conference on Harmonization (ICH), and Guideline for Good Clinical Practice (E6).

3.3 Financial Disclosures

The applicant completed Form FDA 3454 to document financial conflicts of interest and arrangements of clinical investigators. The applicant certified that he has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

In the CMC Review dated 1/23/2013, the reviewing chemist Hamid Shafiei, Ph.D. stated that

> "The applicant of this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product, TRADENAME (desoximetasone)Spray 0.25%."

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The primary CMC review issues in this application were the adequacy of the in-use stability studies and extractables/leachables testing for the proposed container closures. The Agency communicated comments regarding these issues to the applicant in an Advice Letter (74-day letter dated 8/15/2012) and during a teleconference on 3/11/ 2012. In an amendment dated 11/19/ 2012 (SD 18) the applicant submitted study reports for the in-use stability studies which were performed per Agency request. The samples were tested for assay, impurities, isopropyl alcohol (IPA) content, weight-loss and packaging integrity. In addition, the applicant provided a risk assessment for the extractables/leachables studies based on the safety data for the critical components of the to-be-marketed, (b) (4) spray pump used for the topical administration of desoximetasone topical spray 0.25% during the phase 3 trials. The CMC Reviewer concluded the following:

> "Based on review of the information provided in the amendment submitted on 11/19/2012, it is concluded that the proposed container closures are compatible with the drug product. The use of the proposed container closures are further supported by the long-term stability. Therefore, the proposed container closures are considered acceptable."

As of the date of this review, Hamid Shafiei, Ph.D is not able to provide a recommendation for approval of NDA 204141 until the Office of Compliance submits an overall "Acceptable" recommendation regarding the facilities and label/labeling issues are satisfactorily resolved per 21 CFR 314.125(b)(6) & (13).

4.2 Clinical Microbiology

The applicant proposed to omit the routine testing and acceptance criteria for bioburden from drug product release and stability specifications. According to the CMC reviewer the applicant asserted that since this drug product is a non-aqueous product with low water activity and contains more 20% isopropyl alcohol, it will not allow the growth of microorganisms with the exception of certain types of yeasts and molds. Acting Microbiology Team Leader, Bryan S. Riley, Ph.D. indicated that omission of routine bioburden testing from the drug product specification is acceptable. (Communication dated 11/5/2012 in CMC Review dated 1/23/2013).

4.3 Preclinical Pharmacology/Toxicology

The reviewing Pharmacologist Renqin Duan, Ph.D. stated that the applicant has ownership of all the nonclinical toxicology data contained in NDA 178856 (desoximetasone cream 0.25%), NDA 18763(desoximetasone ointment 0.25%) and NDA 18586 (desoximetasone gel 0.05%) to support this NDA submission under Section 505(b)(1) of the Federal Food, Drug, and Cosmetics (FD&C) Act. The applicant submitted a 28- day repeat dose dermal toxicity bridging study in minipigs conducted

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with desoximetasone topical spray and cream, 0.25%, a standard battery of genetic toxicology studies and a subcutaneous fertility study in rats.

No significant differences in toxicological profile were evident following 28 days of dermal administration of desoximetasone topical spray, 0.25% and desoximetasone cream, 0.25% to Göttingen minipigs at the same daily dose level of 0.33 mg/kg. Signs of application site irritation were comparable in the desoximetasone treated groups and vehicle control group.

There was no evidence of mutagenic or clastogenic potential for desoximetasone based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster ovary cell chromosome aberration assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus assay).

There was no evidence of impairment of fertility in male and female Sprague- Dawley rats by subcutaneously doses up to 0.1 mg/kg/day desoximetasone.

Desoximetasone topical spray, 0.25% does not contain any novel excipients. Although impurities 2 and 3 in the proposed drug product are above the International Conference on Harmonization (ICH) qualification threshold, there are no concerns from a pharmacology/toxicology perspective based on the nonclinical data and justification provided by the applicant.

During the Pre-NDA Meeting, the applicant agreed to evaluate the carcinogenic potential of the drug product with a 2 year study in rats as a post-marketing requirement since long-term animal studies have not been performed to evaluate the carcinogenic potential of desoximetasone. On September 28, 2012 the applicant provided the following timeline for the submission:

Final Protocol Submission: 4/30/2015
Trial Completion: 5/31/2017
Final Report Submission: 5/31/2018

The applicant intends to conduct 28 day and 90 day dose range finding studies to determine the appropriate maximum tolerated dose to be used in this 2 year dermal carcinogenicity study. The carcinogenicity study protocols and supporting data will be submitted to the Division for review by the Executive Carcinogenicity Assessment Committee.

The Pharmacology/ Toxicology Reviewer recommended revisions to labeling for Section 8.1, 12.1 and 13.1. The Reviewer proposed text for **Section 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility** which was based on new toxicology data that the applicant provided in this NDA submission.(Underlined language was inserted

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and the ~~strikeout~~ language was deleted from the desoximetasone topical spray, 0.25% labeling).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term animal studies have not been performed to evaluate the carcinogenic potential of (b) (4) Topicort Topical Spray or desoximetasone.

Desoximetasone revealed no evidence of mutagenic or clastogenic potential based on the results of two (b) (4) in *in vitro* genotoxicity tests of (Ames assay and Chinese hamster ovary cell chromosome aberration assay) (b) (4) and (b) (4) one *in vivo* genotoxicity test (mouse bone marrow micronucleus test assay).

No evidence of impairment of male or female fertility was observed at subcutaneous desoximetasone doses up to 0.1 mg/kg/day (0.6 mg/m2/day) in (b) (4) Sprague-Dawley rats. (b) (4)

The Pharmacology/ Toxicology Reviewer concluded:

> "Desoximetasone topical spray, 0.25% is approvable from a pharmacological/ toxicological perspective provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the desoximetasone topical spray, 0.25% label."

See the Pharmacology/ Toxicology Review dated 1/7/2013 and Section 9.1 of this review.

4.4 Clinical Pharmacology

The applicant submitted data from the following 2 Clinical Pharmacology trials in support of the marketing application for desoximetasone topical spray, 0.25%:
1) vasoconstriction trial (Trial 10715005)
2) hypothalamic-pituitary-adrenal (HPA) trial (Trial DSXS-0805).

The applicant conducted Trial 10715005 to assess the vasoconstrictive properties of desoximetasone spray compared with 7 corticosteroid formulations in 32 healthy, non-smoking adults of predominantly African American race (62.5%). The data supported the categorization of desoximetasone topical spray as Class 1/2 since there was no statistically significant difference in response to the reference products of Class 1 and Class 2 in this trial.

The applicant conducted Trial DSXS-0805 to assess potential HPA axis suppression in adults with moderate to severe plaque psoriasis following treatment with

desoximetasone topical spray applied twice daily for 28 days. Investigators enrolled 24 subjects age 18 years and older into one of 2 cohorts: 1) 12 with involvement of 10-15% of their body surface area and 2) 12 with involvement of > 15% of their body surface area. Cosyntropin Stimulation Testing (CST) was conducted at Baseline and Day 28. Investigators collected samples to assess plasma desoximetasone concentration at Baseline, Day 14 and Day 28. However, samples for desoximetasone were tested at unspecified timepoints. See Sections 4.4.2 and 4.4.3 of this review for a discussion of the results of the trial and recommendations for labeling.

The Clinical Pharmacology Reviewer, An-Chi Lu, M.S. Pharm.D. concluded:

> "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." (Clinical Pharmacology Review dated 1/18/2013.)

See Section 9.1 for additional recommendations regarding labeling.

4.4.1 Mechanism of Action

Topical corticosteroids exhibit anti-inflammatory, immunosuppressive, antiproliferative, and vasoconstrictive properties. These effects are mediated by different mechanisms. [1]

- The mechanism of anti-inflammatory activity of the topical corticosteroids is not completely established. Corticosteroids are thought to act by inhibiting the release of phospholipase A2, an enzyme responsible for inducing prostaglandins, leukotrienes, and other derivatives of the arachidonic acid pathway.
- The immunosuppressive effect is mediated by inhibiting humoral factors, leukocyte migration and the functioning of endothelial cells, granulocytes, mast cells, and fibroblasts.
- Antiproliferative effects result from the inhibition of DNA synthesis, fibroblast activity and collagen formation.
- Vasoconstriction is thought to involve the inhibition of endogenous vasodilators (e.g. histamine, bradykinins, and prostaglandins).

The Pharmacology/Toxicology Reviewer recommended the following language to summarize the mechanism of action for Section 12.1 of labeling:

12.1 Mechanism of Action

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1 Valencia IC, Kerdel FA. Chapter 216. Topical Corticosteroids. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, eds. *Fitzpatrick's Dermatology in General Medicine*. 7th ed. New York: McGraw-Hill; 2008

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

4.4.2 Pharmacodynamics

The applicant conducted Trial DSXS-0805 in adult subjects with a diagnosis of moderate to severe plaque psoriasis to provide data regarding systemic exposure and effect of desoximetasone topical spray 0.25% on the hypothalamic-pituitary axis. After excluding data from one laboratory that failed to submit quality control results, twenty-one subjects had evaluable serum cortisol levels and the proportion of subjects demonstrating HPA axis suppression was 8.3% (1/12) in subjects with involvement of 10-15% of BSA, and 22.2% (2/9) in subjects with involvement of > 15% of their BSA. The Clinical Pharmacology Reviewer used the FDA criteria for HPA axis suppression (serum cortisol level ≤18 mcg/dL 30-min post cosyntropin stimulation) to evaluate the data.

The applicant conducted Trial 10715005 to provide an assessment of the relative potency of desoximetasone topical spray 0.25% compared to other marketed corticosteroid products. Two hours after product removal, investigators assessed the degree of vasoconstriction of all corticosteroid products using visual scoring and ChromaMeter assessments at a single timepoint.

The Clinical Pharmacology Reviewer recommended including the findings from trial DSXS-0805 and trial 10715005 in Section 12.2 of labeling as follows:

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)

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression was evaluated in a trial of 24 adult subjects with moderate to severe plaque psoriasis. Topicort Topical Spray was applied twice a day for 28 days. Twenty-one subjects had evaluable serum cortisol levels. The proportion of subjects demonstrating HPA axis suppression was 8.3% (1 out of 12) in subjects having psoriasis involvement of 10-15% body surface area (BSA), and 22.2% (2 out of 9) in subjects having psoriasis involvement of > 15% 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 with available follow-up values, suppression reversed 28 days after the end of treatment.

4.4.3 Pharmacokinetics

Trial DSXS-0805 included the collection of pharmacokinetic (PK) samples from all subjects at Baseline, Day 14 and Day 28 (at least 8 hours after dosing but no timepoints were identified). The mean (Percent Coefficient of Variation) concentration of desoximetasone for all subjects was 449 pg/mL (86%) at Day14 and 678 pg/mL (135%) at Day 28.

The Clinical Pharmacology Reviewer recommended including these results in Section 12.3 Pharmacokinetics as follows:

> Plasma concentrations of desoximetasone were measured at two single random time points in the HPA axis suppression trial in 24 subjects with psoriasis *[see Clinical Pharmacology (12.2)]*. 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.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Phase 1 Dermal Safety Trials

Study Number (Dates of Conduct, Location)	N	Main Goals and Overview of Design	Treatments
HEALTHY ADULT VOLUNTEERS			
Single Application*			
DSXS-0904 (30 Nov – 5 Dec 2009; Rochelle Park, NJ)	38	4-day phototoxicity study: patch test (0.2 mL applied to 2×2-cm area for 24 hours under semi-occlusive patches)	DSXS Spray, 0.25%
			DSXS Spray, 0.05%
			Placebo (Vehicle) Spray
Multiple Applications*			
DSXS-0905 (2 Nov – 18 Dec 2009; Rochelle Park, NJ)	58	6-week photo-allergenicity study (0.2 mL applied to 2×2-cm area for 24 hours under semi-occlusive patches); 6 applications	DSXS Spray, 0.25%
			DSXS Spray, 0.05%
			Positive Control (0.1% SLS)
DSXS-0804 (5 Jan – 18 Feb 2010; Pittsburgh, PA; Houston, TX; Las Vegas, NV)	297	Irritation/induction (0.5 mL applied to 1×1" area for 21 continuous days) followed by sensitization/challenge after a 14-day washout (0.5 mL applied to 1×1" area, at least 2" away from original site, for 44 hours). All application areas were covered by a separate semi-occlusive dressing.	DSXS Spray, 0.25%
			DSXS Spray, 0.05%
			Vehicle (Placebo) Spray
			Clobetasol Spray, 0.05%
			Positive Control (0.1% SLS)
			Negative Control (NS)

Source: NDA 20-4141, Integrated Summary of Safety, modified from Table 3

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Table 5: Phase 1 Vasoconstriction Assay (VCA) Trial

Study Number (Dates of Conduct, Location)	N	Main Goals and Overview of Design	Treatments
HEALTHY ADULT VOLUNTEERS			
Single Application*			
10715005 (19 – 20 Apr 2008; Pittsburgh, PA)	32	Potency ranking vasoconstrictor study: 16-hour non-occluded application (0.01 mL) to forearm with vasoconstriction measured before and 2 hours after application site washing (with two untreated control sites)	DSXS Spray, 0.25%
			Placebo (Vehicle) Spray
			Topicort® Cream, 0.25%
			Topicort LP® Cream, 0.05%
			Clobetasol Spray, 0.05%
			Fluocinonide Ointment, 0.05%
			Mometasone Ointment, 0.1%
			Fluticasone Cream, 0.05%
			Hydrocortisone Cream, 2.5%

Source: Modified from NDA 20-4141, Integrated Summary of Safety pg.16, Table 3

Table 6: Phase 1 HPA Axis Suppression Trial

Study Number (Dates of Conduct, Location)	N	Main Goals and Overview of Design	Treatments
PATIENTS WITH PLAQUE PSORIASIS			
DSXS-0805 (23 Feb – 22 Jun 2010; Simpsonville, SC; Albuquerque, NM; Hot Springs, AR)	24	HPA Axis Suppression and systemic exposure: 28 day regimen (53 applications†)	DSXS Spray, 0.25%

Source: Modified from NDA 20-4141, Integrated Summary of Safety pg.16, Table 3

Table 7: Phase 2 Dose Ranging Trial and Phase 3 Safety and Efficacy Trials

Study ID (Dates of Conduct)	Study Design	No. Enrolled [1] (M/F) [Age Range (yrs)]	No. Completed	Treatments (N)
Phase 2 Study				
DSXS 0906 (20 Nov 2009 – 11 May 2010)	28-day, double-blind[2], vehicle-controlled, randomized, dose- and schedule comparison (1:1:2:2:2), parallel group study	151 (92 / 58) [22 – 82]	148	A: Desoximetasone Spray, 0.05% once daily (30)
				B: Desoximetasone Spray, 0.05% twice daily (31)
				C: Desoximetasone Spray, 0.25% once daily (30)
				D: Desoximetasone Spray, 0.25% twice daily (29)
				E: Vehicle Spray once daily (15)
				F: Vehicle Spray twice daily (15)
Phase 3 Studies				
DSXS 0808 (31 Aug 2010 – 2 Dec 2010)	28-day, double-blind, vehicle-controlled (1:1), randomized, parallel groups	120 (85 / 35) [20 – 80]	119	Desoximetasone Spray, 0.25% twice daily (60)
				Vehicle spray twice daily (60)
DSXS 0914 (7 Sep 2010 – 8 Dec 2010	28-day, double-blind, vehicle-controlled (1:1), randomized, parallel groups	120 (72 / 48) [19 – 81]	120	Desoximetasone Spray, 0.25% twice daily (60)
				Vehicle spray twice daily (60)

Source: NDA 20-4141, Integrated Summary of Efficacy pg.10

5.2 Review Strategy

The review of efficacy was based on data from two Phase 3 double-blind, vehicle controlled, randomized, parallel, multicenter trials (DSXS-0808 and DSXS-0914) comparing desoximetasone topical spray, 0.25% with vehicle spray applied twice per day for 28 days. The study population included a total of 240 subjects age 19 to 81 years with a definitive diagnosis of stable plaque psoriasis involving ≥10% BSA, a total lesion severity score (TLSS) of ≥7 for the target lesion, and a Physician Global Assessment (PGA) score of 3 (moderate), 4 (moderately severe) or 5 (severe) on a 5 point scale at Baseline. One subject who was randomized to desoximetasone topical spray, 0.25% was excluded from the efficacy analysis due to the absence of a post-baseline evaluation.

In addition, the applicant submitted data from a Phase 2 double-blind, vehicle controlled, randomized, parallel, multicenter dose range finding trial (DSXS-0906) comparing desoximetasone topical spray, 0.25% and desoximetasone topical spray, 0.05% with vehicle spray applied for 28 days in subjects age 22 to 82 years with moderate to severe plaque psoriasis. Among the 151 subjects enrolled in the trial DSXS-0906, 44 subjects applied desoximetasone topical spray, 0.25% (29 subjects) or vehicle spray (15 subjects) twice per day.

This reviewer conducted the evaluation of safety on pooled data from subjects who were enrolled in the three vehicle controlled trials (DSXS-0906, DSXS-0808 and DSXS-0914) and who were exposed to desoximetasone topical spray 0.25% or vehicle spray applied twice per day. A total of 284 adult subjects with moderate to severe psoriasis

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were exposed to desoximetasone topical spray 0.25% (149 subjects) or vehicle spray (135 subjects) twice daily for 28 days.

The applicant submitted additional safety data from three dermal safety trials (DXSX-904, DXSX-905 and DXSX-804) and a vasoconstriction trial (1075005) in healthy subjects and an HPA axis suppression trial in subjects with moderate to severe psoriasis involving ≥10% BSA (DXSX-805).

The other sources of safety data were: a review of the worldwide medical literature published from 2004 to December 5, 2011, a review of post-marketing adverse events from the AERS database, line listings from the FDA of adverse events from other manufacturers of desoximetasone products and safety reports for all Topicort formulations submitted to the applicant since the last annual report.

5.3 Discussion of Individual Studies/Clinical Trials

Phase 3 trials
The two Phase 3 trials (DSXS-0808 and DSXS- 0914) were identical with regard to the study design, study population (as defined by the inclusion/exclusion criteria), methodology, and endpoints.

Protocol Numbers:
- **DSXS- 0808**: initiated on 8/31/2010 and completed on 12/2/2010
- **DSXS- 0914**: initiated on 9/7/2010 and completed on 12/8/2010

Title:
Double-Blind, Vehicle Controlled, Randomized, Parallel Design, Multiple-Site Clinical Study to Evaluate the Efficacy and Safety of Desoximetasone 0.25% Topical Spray in Subjects with Moderate to Severe Plaque Psoriasis

Investigators:
There were 9 study sites for each trial. The IRB approved 10 study sites but only 9 enrolled subjects. Investigators and study sites are identified for trials DSXS- 0808 and DSXS- 0914 separately in Table 8 and

Table 9.

Table 8: Principal Investigators and Study Sites DSXS-0808

Site Number	Investigator	Study Site	Subjects Enrolled (n)	Subjects in ITT (n)

1	Christopher A. Moeller, MD	Compliant Clinical Research of Wichita, Inc. 250 North Rock Road, Suite 340 Wichita, KS 67206	12	12
2	Karl G. Heine, MD	Karl G. Heine, MD Dermatology 880 Seven Hills Drive, Suite 150 Henderson, NV 89052	12	12
3	Michael Bukhalo, MD	1100 West Central Road, Suite 200 Arlington Heights, IL 60005	17	17
4	Scott T. Guenthner, MD	The Indiana Clinical Trials Center, PC 1100 Southfield Drive, Suite 1240 Plainfield, IN 46168	12	12
5	Jose Edward Mendez, DO	International Dermatology Research, Inc. 8370 West Flagler Street, Suite 200 Miami, FL 33144	16	16
6	David H. Horowitz, MD	Dermatology Research Associates 1900 Patterson Street, Suite 104 Nashville, TN 37203	19	18
7	John L. Proffitt, MD	John L. Proffitt, MD Compliant Clinical Research, Inc. 153 West 151st Street, Suite 100 Olathe, KS 66061	13	13
8	Harry H. Sharata, MD, PhD	Madison Skin & Research, Inc. 6510 Grand Teton Plaza, Suite 302 Madison, WI 53719	12	12
10	Terry M. Jones, MD	J&S Studies, Inc. 1710 Crescent Pointe Parkway College Station, TX 77845	7	7

Source: NDA 20-4141; Section 5.3.5.1.3; Clinical Study Report DSXS-0808 pp.3-5

Table 9: Principal Investigators and Study Sites DSXS-0914

Site Number	Investigator	Study Site	Subjects Enrolled (n)	Subjects in ITT (n)
1	Stephen M. Schleicher, MD	DermDox 20 North Laurel Street, Suite 2A Hazleton, PA 18201	15	15
2	Alicia D. Bucko, DO, JD	Academic Dermatology Associates 1203 Coal Avenue, S E Albuquerque, NM 87106	18	18
3	David James Kerr, MD	Horizons Clinical Research Center, LLC 4495 Hale Parkway, Suite 101 Denver, CO 80220	18	18
4	Dowling B. Stough, MD	Burke Pharmaceutical Research 3633 Central Avenue, Suite 1 Hot Springs, AR 71913	3	3
5	Zoe Draelos, MD	2444 North Main Street High Point, NC 27262	18	18
6	Allan M. Soo, MD	Premiere Pharmaceutical Research 3316 South McClintock Drive Tempe, AZ 85282	13	13
7	Edward John Primka, III, MD	Dermatology Associates of Knoxville, PC 939 Emerald Avenue, Suite 705 Knoxville, TN 37917	14	14
8	Robert Glenn Brown, MD	North Florida Dermatology Associates, PA 1551 Riverside Avenue Jacksonville, FL 32204	17	17
10	Russell David Mader, MD	Dermatology Associates of Kingsport, PC 2300 West Stone Drive Kingsport, TN 37660	4	4

Source: NDA 20-4141; Section 5.3.5.1.3; Clinical Study Report DSXS-0914 pp.3-5

Objective:

- To evaluate the efficacy and safety of desoxímetasone 0.25% topical spray compared to a vehicle spray in subjects with moderate to severe plaque psoriasis.

Study Population:

- 120 subjects aged 18 years and above with a confirmed diagnosis of stable moderate to severe plaque psoriasis. Eligible subjects must have a minimum of 10% Body Surface Area (BSA) affected, Physicians Global Assessment score (PGA) of 3 or 4 and target lesion at least 5 cm^2 with a plaque elevation score of at least 3 and total lesion severity score (TLSS) of at least 7. Subjects with psoriasis of the scalp/face requiring treatment during the trial were excluded.

Refer to Table 14 for the Baseline disease characteristics for the Phase 3 trials, DSXS-0808 and DSXS- 0914.

Inclusion Criteria:

1. Male or non-pregnant, non-lactating female 18 years or older
2. Signed consent form
3. Females of child bearing potential must abstain from intercourse or use a reliable method of contraception (condom with spermicide, diaphragm, IUD, oral, transdermal, injected or implanted hormonal contraceptives or abstinence)
4. Definitive diagnosis of stable plaque psoriasis involving ≥10% BSA
5. Total lesion severity score (TLSS) of ≥7 for the target lesion
6. Physician Global Assessment (PGA) score of 3 (moderate) or 4 (severe) at Baseline
7. Target lesion must not be on the face, genitals or intertriginous area
8. Target Lesion area of at least 5 cm^2
9. Plaque elevation Score ≥3

Exclusion Criteria:

1. Under age 18
2. Females who are pregnant, nursing or planning to become pregnant or females of child-bearing potential who are sexually active and not prepared to use appropriate contraceptive methods
3. BSA<10%
4. TLSS of <7 for the target lesion
5. Score of <3 for the individual sign of plaque elevation for the target lesion
6. Target lesion area <5 cm
7. PGA<3 (moderate) or >4 (severe) at Baseline for overall disease severity
8. Diagnosis of other types of psoriasis (e.g. acute, guttate, erythrodermic, exfoliative or pustular) or psoriasis of the scalp/face requiring treatment during the trial
9. History of psoriasis unresponsive to topical corticosteroids

10. Possessed other dermatologic conditions that may interfere with the assessment of the signs or symptoms of psoriasis
11. History of allergy or insensitivity to corticosteroids
12. History of chronic infectious disease, or other systemic disorder that would place the subject at undue risk
13. Receiving or has received radiation therapy, anti-neoplastic agents or immunosuppressant medication within 4 weeks
14. Treatment with systemic anti- psoriatic or phototherapy in the last 8 weeks
15. Treatment with a biologic therapy within the last 12 weeks or 5 half-lives which ever is less
16. Treatment with systemic corticosteroids in the last 4 weeks
17. Treatment with hormonal contraceptives for less than 1 month
18. Treatment with any topical product for psoriasis except anti-psoriatic shampoo (allowed) within the last 2 weeks
19. Treatment with a research drug within 30 days
20. Anticipated non-compliance
21. Previous participation in this study

Study Plan:
This was a double-blind, vehicle-controlled, randomized, parallel group, multicenter trial comparing desoximetasone topical spray, 0.25% with vehicle spray in subjects with moderate to severe plaque psoriasis. One hundred and twenty subjects were randomly assigned 1:1 to desoximetasone topical spray or vehicle spray. Subjects were instructed to apply desoximetasone topical spray or vehicle spray twice daily (approximately 12 hours apart) for 28 days to all affected areas and rub in gently and completely.

Assessments which were recorded at each visit (Day 1, Day 7, Day 14 and Day 28) included: signs and symptoms of psoriasis, adverse events (including local adverse events), concomitant medications, compliance, % BSA, PGA and Total Lesion Severity Score TLSS. Study personnel provided subjects with daily dosing diaries and dispensed a new 100 ml bottle of study product at each visit with instructions to encourage compliance. At each visit, investigators queried subjects regarding any changes in their medical status, recorded the amount of product applied and assessed subject compliance with the protocol.

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Table 10: Trial Procedures

PROCEDURE	VISIT 1 Screening/ Randomization Day 1	VISIT 2 Interim Visit Day 7 ±2days	VISIT 3 Interim Visit Day 14 ±2 days	VISIT 4 End of Study Day 28 ±2 days
Informed Consent	X			
Medical History	X			
Physical Exam	X			
Vital Signs	X			X
Dermatological Assessment	X	X	X	X
% BSA Assessment	X	X	X	X
PGA Score	X	X	X	X
TLSS Score	X	X	X	X
Pregnancy Test	X			X
Concomitant Medication	X	X	X	X
Collect/Dispense Study Medication	X		X	X
Provide/Review Patient Dosing Diary	X	X	X	X
Adverse Events		X	X	X
Evaluation of Patient Compliance to the Protocol		X	X	X

Source: NDA 20-4141; Section 5.3.5.1.4; Protocol DSXS-0808 and DSXS- 0914; pg. 9

<u>Prohibited concomitant medications</u>

- Any prescription or over-the-counter (OTC) topical, systemic, phototherapy, or biological medications or treatments for psoriasis.
- Any non-steroidal immunosuppressants (by any route of administration).
- Use of non-sedating anti-histamines.
  - The use of sedating anti-histamines (e.g. diphenhydramine) was acceptable if the subject remained on a stable dose for at least 14 days prior to enrollment and throughout the study.
- Any systemic steroid drug use {with the exception of hormone replacement therapy (HRT) and contraceptives}.
  - Female subjects using hormonal contraceptives or HRT should remain on a stable dose for at least 28 days prior to the study and during the study.
- New regimens of inhaled corticosteroids.
  - Inhaled corticosteroids were permissible, provided that subjects remain on a stable regimen for at least 2 weeks prior to the study and during the study.
- Any other treatments, prescription or over-the-counter products for the treatment of any other dermatological condition including; topical corticosteroids,

antibacterial, medicated and/or astringent washes, soaps, pads or moisturizers during the study.
- Use of high strength (20% or above) alpha-hydroxy acid or any kind of peel or other procedures on the treatment area (ex. laser hair removal) during the study.

Other restrictions:
- Avoid environmental conditions that may exacerbate the disease (e.g. wind and sun exposure. Neutrogena SPF 45 sunscreen was provided when sun exposure was unavoidable.)
- Do not occlude treatment area.
- Use standardized moisturizing agent for dry skin (Eucerin lotion provided).

Subject Removal from the Study
- Subject decision: for any reason at any time
- Investigator decision for the following reasons:
  - Worsening signs/symptoms
  - Development of an intercurrent condition /complication that could affect subject safety or the validity of the evaluation
  - Signs and symptoms of possible HPA axis suppression
  - Non-compliance
  - Protocol deviations/violations

Efficacy Evaluation
Co-primary efficacy endpoints:
- **Clinical success**: defined as the proportion of subjects in each treatment group with a PGA score of 0 or 1 at Day 28
- **Treatment success**: defined as the proportion of subjects in each treatment group with a target lesion score of 0 or 1 for erythema, scaling and plaque elevation at Day 28

Secondary efficacy endpoints:
- Mean change from Baseline in TLSS at Day 28
- Mean change from Baseline in PGA at Day 28
- Mean change from Baseline in % BSA at Day 28

Scales used in the assessment of efficacy

Table 11: Physician's Global Assessment Scale to Grade Global Severity

Physician's Global Assessment (PGA)	
0	Clear. No psoriatic lesions, i.e. no plaque elevation , no erythema, no induration, no scaling .

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1	Almost clear. No more than minimal scaling and minimal residual erythema. No more than minimal plaque elevation just above normal skin level
2	Mild. Scaling present although not extensive. Plaque elevation discernable but not pronounced, erythema generally light red in color.
3	Moderate. Scaling easily observed with red erythema. Plaque elevation distinct and elevated with rounded, sloping edges
4	Severe. Scaling is coarse and thick. Erythema is dark red. Plaque elevation has hard edges.
5	Very Severe. Coarse scaling with pronounced cracking and fissures. Erythema is dark red with induration. Plaques are markedly elevated with sharp and hard edges.

Source: NDA 20-4141; Section 5.3.5.1.4; Protocol DSXS-0808 and DSXS- 0914; pg. 38

Table 12: Total Lesion Severity Scale to Grade the Target Lesion

Total Lesion Severity Score (TLSS)			
Score	**Scaling**	**Erythema**	**Plaque Thickness**
0	Clear. No evidence of scaling	Clear. No evidence of erythema	Clear. No evidence of plaques above surrounding normal skin
1	Almost clear. Occasional fine scales	Almost clear. Pink coloration	Almost clear. Minimal plaque elevation. Slight but definite elevation above surrounding normal skin
2	Mild. Slight but definite roughness	Mild. Light red coloration	Mild. Mild plaque elevation
3	Moderate. Moderate roughness, coarse scaling	Moderate. Moderate redness, but not dark	Moderate. Moderate plaque elevation
4	Severe. Marked roughness, thick scaling	Severe. Dark red coloration	Marked. Marked plaque elevation
5	Very severe. Very thick scales covering extensive areas	Very Severe. Very dark red coloration	Severe. Severe plaque elevation

Source: Modified from NDA 20-4141; Section 5.3.5.1.4; Protocol DSXS-0808 and DSXS- 0914; pg. 39

Body Surface Area Calculation

- Total Body Surface Area (BSA) in meters squared m^2 =

Reference ID: 3252617

((height (cm) x weight (kg)) /3600)$^{1/2}$
- % Body Surface Area Affected: the "Rule of Nine" was used

Safety:
- Safety assessments included: AEs summarized by severity, frequency and relationship to the study drug for each treatment group, vital signs at every visit and pregnancy testing of all female subjects of child bearing potential at Baseline and at the last study visit. Investigators queried subjects regarding any changes in their medical status, recorded the amount of product applied and assessed subject compliance with the protocol at each visit.

Statistical Analysis
- Blinding: Randomization was performed according to a computer-generated randomization scheme which generated a unique four-digit randomization number for each subject kit. Each subject was assigned one subject number. All personnel were blinded to the subject assignment.
- Intent- to- treat (ITT) analysis set: all subjects who were exposed to at least one dose of the study drug and returned for a follow-up visit.
- Imputation Method: last observation carried forward (LOCF).

Amendments to the Protocols: DSXS-0808/ DSXS-0914
Amendment 1 Date 07/21/10: key changes to the protocol
- The efficacy analysis section of the statistical methods (section 9.6.1.3) was revised to clarify the planned analysis of the primary endpoints and to address multiplicity in the secondary endpoints.

Refer to Section 6 of this review for the results of the efficacy assessment and Section 7 of this review for the results of the safety assessment for the Phase 3 trials (DSXS-0808/ DSXS-0914).

Phase 2 trial

The **Phase 2 trial (DSXS- 0906**) was identical to the 2 Phase 3 trials (DSXS-0808 and DSXS- 0914) with regard to study population (as defined by the inclusion/exclusion criteria), duration of treatment, and endpoints. However, the objective of the trial was to identify the optimal dose and dosing regimen by comparing two concentrations of desoximetasone topical spray (0.05% and 0.25%) and two dosing regimens (once or twice daily applications) with vehicle spray (applied once or twice daily) for 28 days.

Protocol Number: DSXS -0906 (initiated 11/20/2009 and completed 5/11/2010)

Title:

A Double-Blind, Vehicle-Controlled, Randomized, Dose Ranging, Multiple-Site Clinical Study to Evaluate the Efficacy and Safety of Two Desoximetasone Topical Sprays (0.05% and 0.25%) in Patients with Moderate to Severe Psoriasis

Table 13: Principal Investigators and Study Sites DSXS-0906

Site Number	Investigator	Study Site	Subjects Enrolled (n)	Subjects in ITT (n)
1	Christopher A. Moeller, MD	Compliant Clinical Research of Wichita, Inc. 250 North Rock Road, Suite 340 Wichita, KS 67206	30	30
2	John L. Proffitt, MD	John L. Proffitt, MD Compliant Clinical Research, Inc. 153 West 151st Street, Suite 100 Olathe, KS 66061	20	20
3	Alicia D. Bucko, DO, JD	Academic Dermatology Associates 1203 Coal SE Albuquerque, NM 87106	16	15
4	Jose Edward Mendez, DO	International Dermatology Research, Inc. 8370 West Flagler Street, Suite 200 Miami, FL 33144	40	40
5	Robert Bourmork Rhoades, MD	Medical Parameters 4485 Columbia Road Martinez, GA 30907	8	8
6	Patricia Peeples Westmoreland, MD	Palmetto Clinical Trials Services,LLC 611 NE Main Street, St A Simpsonville, SC 29681	18	18
7	David H. Horowitz, MD	Dermatology Research Associates 1900 Patterson Street, Suite 104 Nashville, TN 37203	19	19

Source: NDA 20-4141; Section 5.3.5.1.3; Clinical Study Report DSXS-0906 pp.3-5

Objective:

- To evaluate the efficacy and safety of two dosing regimens of desoximetasone 0.05% and 0.25% topical sprays as compared to a vehicle spray in subjects with moderate to severe plaque psoriasis.

Study Population:

- 151 male and female subjects aged 18 years and above with a confirmed diagnosis of stable moderate to severe plaque psoriasis were enrolled. Eligible subjects had ≥ 10% Body Surface Area (BSA) affected, Physicians Global Assessment score (PGA) of 3 or 4 and target lesion at least 5 cm^2 with a plaque elevation score of at least 3 and total lesion severity score (TLSS) of ≥ 7.

Number of Patients	
Treatment Group	N
once-a-day with 0.05%	30
twice-a-day with 0.05%	31
once-a-day with 0.25%	30
twice-a-day with 0.25%	29
once-a-day with vehicle	15
twice-a-day with vehicle	15
Total	**150**

Source: NDA 20-4141; Section 5.3.5.1.4: Clinical Study Report DSXS-0906 p. 6

Key Inclusion Criteria:

- Male or non-pregnant, non-lactating female 18 years or older
- Females of child bearing potential must abstain from intercourse or use a reliable method of contraception
- Definitive diagnosis of stable plaque psoriasis involving ≥10% BSA
- Total lesion severity score (TLSS) of ≥7 for the target lesion
- Physician Global Assessment (PGA) score of 3 (moderate), 4 (moderately severe) or 5 (severe) at Baseline
- Target lesion must not be on the face, genitals or intertriginous area

Key Exclusion Criteria:

- History of psoriasis unresponsive to topical corticosteroids
- Possessed other dermatologic conditions that may interfere with the assessment of the signs or symptoms of psoriasis
- History of allergy or insensitivity to corticosteroids
- History of chronic infectious disease, or other systemic disorder that would place the subject at undue risk
- Treatment with systemic anti psoriatic or phototherapy in the last 12 weeks
- Treatment with a biologic therapy within the last 12 weeks or 5 half-lives which ever is less
- Treatment with systemic corticosteroids in the last 4 weeks
- Treatment with any topical product for psoriasis except shampoo within the last 2 weeks

Study Plan:
This is a double-blind, vehicle-controlled, randomized, dose ranging, multicenter clinical trial to evaluate the efficacy and safety of two desoximetasone topical sprays (0.05% and 0.25%) in subjects with moderate to severe psoriasis. Subjects were randomly assigned to 6 treatment groups:

A: 30 subjects treated daily with 0.05% desoximetasone topical spray
B: 30 subjects treated twice per day with 0.05% desoximetasone topical spray
C: 30 subjects treated daily with 0.25% desoximetasone topical spray
D: 30 subjects treated twice per day with 0.25% desoximetasone topical spray
E: 15 subjects treated daily with vehicle spray
F: 15 subjects treated twice per day with vehicle spray

Subjects applied desoximetasone topical spray or vehicle spray gently to all affected areas once or twice per day for 28 days. Subjects were assessed for signs and symptoms of psoriasis, adverse events, concomitant medications, %BSA, PGA and TLSS on Day 1, Day 7, Day 14 and Day 28. Study personnel provided subjects with daily dosing diaries and dispensed a new 100 ml bottle of study product at each visit with instructions to encourage compliance. At each visit, investigators queried subjects regarding any changes in their medical status, recorded the amount of product applied and assessed subject compliance with the protocol.

The study procedures were the same for Trial DSXS-0906, Trial DSXS-0808 and Trial DSXS-0914. Refer to Table 10 for a summary of the trial procedures.

Co-primary efficacy endpoints:

- **Clinical success**: defined as the proportion of subjects in each treatment group with a PGA score of 0 or 1 at day 28
- **Treatment success**: defined as the proportion of subjects in each treatment group with a target lesion score of 0 or 1 for erythema, scaling and plaque elevation at day 28

The secondary efficacy endpoints

- Mean change from Baseline in PGA at Day 28
- Mean change from Baseline in TLSS at Day 28
- Mean change from Baseline in % BSA at Day 28

This trial was used to power the Phase 3 trials and to optimize the treatment regimen. Thus, the same scales (PGA and TLSS) were used in this trial (DSXS-0906) and in the Phase 3 trials (DSXS-0808/ DSXS-0914). Refer to Table 11 and Table 12.

Safety Evaluation

Reference ID: 3252617

Investigators recorded adverse events (AEs) and evaluated the potential relationship to the study drug. The safety assessments included: a physical examination (Screening), vital signs (Screening and End of Study) and pregnancy testing in females of child bearing potential (FCBP). Subjects were queried regarding any changes in their medical status.

Table 14: Efficacy Analysis: Used to Design Phase 3

Analysis of Primary Efficacy Endpoints			
	N	Clinical Success Rate	Treatment Success Rate
0.05% once a day	30	13.33 %	6.67 %
0.05% twice a day	30	10.00 %	16.67 %
0.25% once a day	29	20.69 %	34.48 %
0.25% twice a day	29	37.93 %	31.03 %
Vehicle once a day	15	6.67 %	6.67 %
Vehicle twice a day	15	6.67 %	6.67 %
Primary Endpoint: Proportion of Patients considered a Clinical Success at Day 28			
Superiority over Vehicle		Corrected Z-score	One-sided p-value
0.05% once a day vs. vehicle once a day		0.1863	0.4261
0.05% twice a day vs. vehicle twice a day		0.1971	0.4219
0.25% once a day vs. vehicle once a day		0.9054	0.1826
0.25% twice a day vs. vehicle twice a day		2.3662	0.0090*

Source: NDA 20-4141; Section 5.3.5.1.4: Clinical Study Report DSXS-0906 p. 9

6 Review of Efficacy

Efficacy Summary

The applicant submitted data from 2 Phase 3 trials (DSXS-0808/ DSXS-0914) to support the efficacy of desoximetasone topical spray, 0.25% for the treatment of plaque psoriasis of the body in patients 18 years of age or older The applicant conducted 2 multicenter, randomized, double-blind, vehicle- controlled clinical trials enrolling a total of 240 subjects aged 18 years and older with moderate to severe plaque psoriasis of the body. One subject who was randomized to desoximetasone topical spray, 0.25% was excluded from the efficacy analysis due to the absence of a post-baseline evaluation. In both trials, subjects were randomized 1:1 to apply desoximetasone topical spray or vehicle spray to the affected areas twice daily for 4 weeks.

Enrolled subjects had a minimum body surface area of involvement of 10%, a Physician's Global Assessment score (PGA) of 3 (moderate) or 4 (severe), and a target lesion at least 5 cm^2 with a plaque elevation score of at least 3 and Total Lesion Severity Score (TLSS) of at least 7. Investigators excluded subjects with psoriasis of the

scalp/face requiring additional treatment during the trial. Subjects were evaluated using a 6- category PGA scale and a 6-category TLSS scale ranging from 0 (clear) to 5 (very severe).
Efficacy was assessed at Week 4 as the proportion of subjects who were considered a Clinical Success ("clear" or "almost clear" according to the PGA scale) AND a Treatment Success for the Target Lesion ("clear" or "almost clear" for each of the three signs of erythema, scaling and plaque elevation). Desoximetasone topical spray, 0.25% was statistically superior to vehicle spray for the treatment of plaque psoriasis of the body in both Phase 3 trials.

In trial DSXS-0808, 30.5% of subjects achieved Clinical Success and 39.0% achieved Treatment Success in the desoximetasone topical spray group while 5.0 % of subjects achieved Clinical Success and 6.7% achieved Treatment Success in the vehicle spray group. In trial DSXS-0914, 53.3% of subjects achieved Clinical Success and 53.3% achieved Treatment Success in the desoximetasone topical spray group while 18.3 % of subjects achieved Clinical Success and 16.7% achieved Treatment Success in the vehicle spray group.

The secondary endpoints that were used to assess efficacy in Phase 3 trials were defined as: the Mean change from Baseline in TLSS at Day 28, the Mean change from Baseline in PGA at Day 28 and the Mean change from Baseline in % BSA at Day 28. In both Phase 3 trials, a greater proportion of subjects achieved a significant mean change from Baseline at Day 28 in PGA score, TLSS, and % BSA affected in the desoximetasone topical spray treatment group than the vehicle spray treatment group.

Analysis of treatment effect by age (≤65 versus >65) and race (White versus Non-white) was cofounded by the limited numbers of Non-white subjects and subjects > 65 years old. The trends which were evident from the data were: subjects >65 years of age showed greater treatment effect than subjects 18-65 years of age and African American subjects showed a greater treatment effect than White subjects in both trials.

In conclusion the applicant established the efficacy of desoximetasone topical spray, 0.25% compared with vehicle spray for the treatment of plaque psoriasis of the body in patients 18 years of age or older.

6.1 Indication

The proposed indication for TRADENAME (desoximetasone) Topical Spray, 0.25% is: "the (b) (4) plaque psoriasis in patients 18 years of age or older".

Reference ID: 3252617

6.1.1 Methods

The applicant submitted data from 2 adequate and well-controlled Phase 3 trials (DSXS-0808/ DSXS-0914) to support the efficacy of desoximetasone topical spray, 0.25% for the treatment of moderate to severe plaque psoriasis in patients 18 years of age or older. The applicant submitted additional efficacy data for the proposed dosing regimen in a Phase 2 dose range finding trial DSXS-0906.

The 2 Phase 3 trials were double-blind, vehicle-controlled, randomized, parallel group, multicenter trials comparing desoximetasone topical spray with vehicle spray applied twice per day for 28 days. A total of 240 adult subjects with a confirmed diagnosis of stable moderate to severe plaque psoriasis enrolled in the Phase 3 trials. In trial DSXS-0808, one subject who was randomized to desoximetasone topical spray was excluded from the efficacy analysis due to the absence of a post-baseline evaluation. Eligible subjects had a minimum of 10% Body Surface Area (BSA) affected, Physicians Global Assessment score (PGA) of 3 or 4 and target lesion at least 5 cm^2 with a plaque elevation score of at least 3 and total lesion severity score (TLSS) of at least 7. Subjects with psoriasis of the scalp/face requiring treatment during the trial were excluded.

Thirty six subjects participated in both the Phase 2 trial and one of the Phase 3 trials.[2] The interval between the treatments administered to these subjects during the first and second trials was greater than 148 days. All subjects who participated in 2 trials met the enrollment criteria for both trials with regard to disease severity and percent BSA involvement with psoriasis. Data from these subjects was included in the efficacy analysis. No subject participated in 2 Phase 3 trials. Refer to Table 24 of this review and the Statistical Review by Carin Kim dated 1/16/2013.

6.1.2 Demographics

The Baseline demographic characteristics of the study population included in the Phase 3 trials (DSXS-0808, DSXS-0914) are summarized in Table 15. The treatment groups in each Phase 3 trial were similar with regard to age, sex, race, ethnicity and BSA. The majority of the subjects were male (58-70%), white (≥ 93%) and not Hispanic/Latino (≥83%). In all treatment groups, the mean age was approximately 50 years (range 48-54 years).

Table 15: Demographic Data for the Phase 3 Trials

	DSXS-0808		DSXS-0914	
	desoximetasone, topical spray n (%)	vehicle spray n (%)	desoximetasone, topical spray n (%)	vehicle spray n (%)

2 The applicant identified 35 subjects participating in the Phase 2 trial and one of the Phase 3 trials. An additional subject was identified during the review.

ITT* Subjects	59	60	60	60
Age (years)				
<65	50 (83.3%)	43 (71.7%)	51 (85.0%)	44 (77.3%)
≥65	9 (16.7%)	17 (28.3%)	9 (15.0%)	16 (22.7%)
range	22-76	20-80	19-76	23-81
Sex				
Female	17 (28.8%)	17 (28.3%)	23 (38.3%)	25 (41.7%)
Male	42 (71.2%)	43 (71.7%)	37 (61.7%)	35 (58.3%)
Race				
White	57 (96.6%)	57 (95.0%)	57 (95.0%)	56 (93.3%)
Black	2 (3.9%)	2 (3.3%)	2 (2.3%)	0
Asian	0	1 (1.7%)	0	2 (3.3%)
Other*	0	0	1 (1.7%)	2 (3.3%)
Ethnicity				
Hispanic	8 (13.3%)	8 (13.3%)	11 (18.3%)	10 (16.7%)
Not Hispanic	51 (86.7%)	52 (86.7%)	49 (81.7%)	50 (83.3%)

Source: NDA 204141, Integrated Summary of Efficacy, Table 2, pg 16
*ITT analysis set: all randomized subjects who had at least one post-baseline assessment
*Other includes American Indian/Alaskan Native, Native Hawaiian or Other Pacific Islander.
Source: NDA 204141, Integrated Summary of Efficacy, Table 2, pg 16 and Statistical Review by Carin Kim

The Baseline disease characteristics by treatment group for the Phase 3 trials (DSXS-0808, DSXS-0914) are presented in Table 16. The %BSA, distribution of PGA scores (3 or 4) and TLSS were comparable between treatment groups in each trial. The majority of subjects had a PGA score of 3 and a TLSS of 10. Subjects enrolled in the Phase 3 trials had a %BSA of 16 to18.

Table 16: Baseline Disease Characteristics for the Phase 3 Trials

	DSXS-0808		**DSXS-0914**	
	desoximetasone, topical spray n (%)	**vehicle spray** n (%)	**desoximetasone, topical spray** n (%)	**vehicle spray** n (%)
ITT* Subjects	59	60	60	60
Baseline %BSA affected				
mean±SD	15.6±9.1	16.0±10.4	17.8±14.3	15.7±9.4
range	10-60	10-70	10-86	10-70
Baseline PGA				
3 (moderate)	44 (74.6%)	44 (73.3%)	38 (63.3%)	40 (66.7%)
4 (severe)	15 (25%)	16 (26.7%)	22 (36.7%)	19 (31.7%)
5 (very severe)	0-	-0	-0	1 (1.7%)
Baseline TLSS				
mean±SD	9.5±1.5	9.4±1.2	10.0±1.6	10.0±1.6

range	7-15	7-12	7-14	7-15
Baseline target lesion size				
mean±SD	41.5±39.5	38.02±33.1	50.3±100.7	57.4±87.4
range	6-209	5-196	6-651	6-565

Source: NDA 204141, Integrated Summary of Efficacy, Table 3, pg 17 and Statistical Review by Carin Kim, Ph.D.
*ITT analysis set: all randomized subjects who had at least one post-baseline assessment

6.1.3 Subject Disposition

A total of 24 subjects withdrew from the Phase 3 trials: 11 subjects withdrew from trial DSXS-0808 and 13 subjects withdrew from trial DSXS-0914. The percentage of subjects who withdrew was greater in the vehicle spray treatment group of each trial (10.0% from DSXS 0808, 11.7% from DSXS 0914) than from the desoximetasone spray treatment group of each trial (8.3% from DSXS 0808, 10.0% from DSXS 0914).
The percentage of subjects who withdrew as a result of adverse events including exacerbation of psoriasis ranged from 1.7% to 3.3% and was greater in the vehicle treatment groups. Refer to Section 7.3.3 for narratives regarding subjects who withdrew due to adverse events.

The most common reasons for withdrawal from the desoximetasone topical spray treatment groups were change in scheduled visit and insufficient study medication. In comparison, the most common reasons for withdrawal from the vehicle spray treatment groups were exacerbation of psoriasis, withdrawal of consent and change in scheduled visit. Refer to Table 17 for a summary of subject disposition in the Phase 3 trials.

Table 17: Subject Disposition in the Phase 3 Trials

	Study and Treatment Group			
	DSXS 0808		DSXS 0914	
	DSXS 0.25% *b.i.d.*	Vehicle Spray *b.i.d.*	DSXS 0.25% *b.i.d.*	Vehicle Spray *b.i.d.*
Total N Randomized and Treated	60	60	60	60
Total N (%) Discontinuing	5 (8.3%)	6 (10.0%)	6 (10.0%)	7 (11.7%)
Reason for Discontinuation				
Adverse event – other	0	0	0	1 (1.7%)
Adverse event –psoriasis	1 (1.7%)	2 (3.3%)	0	1 (1.7%)
Enrolled in error	0	0	0	1 (1.7%)
Insufficient therapeutic response/Treatment failure	1 (1.7%)	1 (1.7%)	1 (1.7%)	0
Lost to follow-up	1[1] (1.7%)	1 (1.7%)	1 (1.7%)	0
Other – change in scheduled visit	0	0	3 (5.0%)	3 (5.0%)
Other – patient ran out of study medication	2 (3.3%)	0	0	0
Withdrew consent	0	2 (3.3%)	1 (1.7%)	1 (1.7%)

Source: NDA 204141, Section 2.7, Table 2.7.3.5

The efficacy analysis included 23 of the 24 subjects who withdrew from the Phase 3 trials. The only subject who was not included in the analysis (Patient 0808-06-034) did not return after the baseline visit. The 7 subjects who discontinued due to insufficient therapeutic response or exacerbation of psoriasis were included in the analyses as clinical / treatment failures. The following Table displays the other reasons for subject withdrawal among the remaining 16 subjects.

Table 18: Reason for Subject Withdrawal

ISE No.	Treatment Group	Baseline Severity		Days on Drug	Reason for DC	Response		Included in Analysis?
		TLSS	PGA			Clinical	Treatment	
0808-03-176	DSXS 0.25% *b.i.d.*	13	4	22	Ran out of meds[1]	No	No	Yes
0808-03-178	DSXS 0.25% *b.i.d.*	10	4	15	Ran out of meds[2]	No	No	Yes
0808-05-155	Vehicle	10	3	15	Withdrew consent	No	No	Yes
0808-06-030	Vehicle	10	3	19	Lost to follow-up	No	No	Yes
0808-06-170	Vehicle	10	4	13	Withdrew consent	No	No	Yes
0914-01-027	Vehicle	9	3	21	Inability to keep appt	No	No	Yes
0914-01-028	Vehicle	9	3	21	Inability to keep appt	No	No	Yes
0914-03-059	DSXS 0.25% *b.i.d.*	9	4	22	Visit 4 scheduled outside window[3]	Yes	Yes	Yes
0914-03-070	DSXS 0.25% *b.i.d.*	8	3	8	Lost to follow-up	No	No	Yes
0914-04-075	Vehicle	12	3	8	Adverse event	No	No	Yes
0914-07-003	DSXS 0.25% *b.i.d.*	9	3	11	Withdrew consent	No	No	Yes
0914-07-181	Vehicle	9	3	8	Withdrew consent	No	No	Yes
0914-08-103	Vehicle	15	5	15	Enrolled in error[4]	No	No	Yes
0914-10-151	Vehicle	11	4	22	Visit 4 scheduled outside window	No	No	Yes
0914-10-152	DSXS 0.25% *b.i.d.*	9	3	24	Visit 4 scheduled outside window	No	No	Yes
0914-10-153	Vehicle	12	4	22	Visit 4 scheduled outside window	No	No	Yes

4 This subject was a screening failure but was treated for 14 days prior to recognizing the error.
Source: NDA 204141 Integrated Summary of Efficacy pg. 20

6.1.4 Analysis of Primary Endpoint(s)

The analysis of efficacy was based on the following co-primary endpoints:

- **Clinical success**: defined as the proportion of subjects in each treatment group with a PGA score of 0 or 1 at Day 28
- **Treatment success**: defined as the proportion of subjects in each treatment group with a target lesion score of 0 or 1 for erythema, scaling and plaque elevation at Day 28

The applicant conducted the primary analysis on the Intent- to- treat (ITT) analysis set which included all subjects who were randomized, exposed to at least one dose of the

study treatment and returned for evaluation. The imputation method used to account for missing data was the "last observation carried forward" (LOCF). Data regarding the percentage of subjects achieving success on the co-primary endpoints is presented in Table 19. In both Phase 3 trials, a greater proportion of subjects achieved Clinical and Treatment Success in the desoximetasone topical spray treatment group than the vehicle spray treatment group. A greater proportion of subjects enrolled in trial DSXS-0914 achieved Clinical and Treatment Success than enrolled in trial DSXS-0808 in both treatment groups.

Table 19: Percentage of Subjects Achieving Success on the Primary Efficacy Endpoint

	desoximetasone topical spray	vehicle spray	p-value
Trial DSXS-0808			
Clinical Success	18/59 (30.5%)	3/60 (5.0%)	0.0003
Treatment Success	23/59 (39.0%)	4/60 (6.7%)	<0.0001
Trial DSXS-0914			
Clinical Success	32/60 (53.3%)	11/60 (18.3%)	<0.0001
Treatment Success	18/59 (30.5%)	10/60 (16.7%)	<0.0001

Source: NDA 204141 Section 2.7 Clinical Summary and Statistical Review by Carin Kim, Ph.D.
P-value is calculated from two-sided continuity corrected Z-test.
* all 36 common subjects across the two Phase 3 trials are included
* Investigators identified ≥ 5 cm^2 plaque localized to the trunk or extremities (not face, groin or intertriginous area) with a Baseline total lesion severity score (TLSS) of ≥7 and plaque elevation score ≥3

All efficacy data was reanalyzed using SAS and the results confirmed by the biostatistician. Refer to Section 9.1 of this review for labeling recommendations.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints that were used to assess efficacy in the Phase 3 trials were:

- Mean change from Baseline in TLSS at Day 28
- Mean change from Baseline in PGA at Day 28
- Mean change from Baseline in % BSA at Day 28

Table 20: Secondary Endpoint Analysis: DSXS-0808 and DSXS-0914

	desoximetasone topical spray Mean±SD	vehicle spray Mean±SD	p-value[(1)]
Study 0808	N=59	N=60	
Mean change from baseline in TLSS	4.73±3.08	1.93±1.96	<0.0001
Mean change from baseline in PGA	1.14±0.90	0.50±0.68	<0.0001

Mean change from baseline in %BSA affected	2.24±3.79	0.37±2.05	0.0011
Study 0914			
Mean change from baseline in TLSS	6.18±3.13	3.02±2.97	<0.0001
Mean change from baseline in PGA	1.73±1.06	0.85±0.94	<0.0001
Mean change from baseline in %BSA affected	3.47±4.74	1.27±4.23	0.0083

Source: NDA 204141 Section 2.7 Clinical Summary Table 2.7.3:9 and Statistical Review by Carin Kim

In both Phase 3 trials, a greater proportion of subjects achieved a significant mean change from Baseline at Day 28 in PGA score, TLSS, and % BSA affected in the desoximetasone topical spray treatment group than the vehicle spray treatment group.

6.1.6 Other Endpoints

No other endpoints were evaluated.

6.1.7 Subpopulations

Analysis of treatment effect by age (≤65 versus >65) and race (White versus Non-white) was cofounded by the limited numbers of Non-white subjects and subjects > 65 years old. Although the significance is unclear given the limitations of the database, the following trends are evident from the data:

- subjects >65 years of age showed greater treatment effect than subjects 18-65 years of age
- African American subjects showed a greater treatment effect than White subjects in both trials.

Table 21: Proportion of Subjects with Clinical Success at Day 28 by Gender, Race and Age

	DSXS-0808		DSXS-0914	
	desoximetasone, topical spray	vehicle spray	desoximetasone, topical spray	vehicle spray
ITT [1] Subjects	59	60	60	60
Age				
18-65	14/50 (28.0%)	1/44 (2.3%)	26/52 (50.0%)	8/45 (17.8%)
>65	4/9 (44.4%)	2/16 (12.5%)	6/8 (75.0%)	3/15 (20.0%)
Sex				
Female	6/17 (35.3%)	1/17 (5.9%)	10/23 (43.5%)	4/25 (16.0%)

Male	12/42 (28.6%)	2/43 (4.7%)	22/37 (59.5%)	7/35 (20.0%)
Race				
Asian	-0	0/1 (0%)	-0	0/2 (0%)
Black	1/2 (50%)	0/2 (0%)	1/2 (50%)	-0
White	17/57 (29.8%)	3/57 (5.3%)	30/57 (52.6%)	11/56 (19.6%)
Native American	-0	-0	-0	0/1 (0%)
Other Pacific	-0	-0	1/1 (100%)	0/1 (0%)

Source: Statistical Review by Carin Kim, Ph.D., Table 14

Table 22: Proportion of Subjects with Treatment Success at Day 28 by Gender, Race and Age

	DSXS-0808		DSXS-0914	
	desoximetasone, topical spray	vehicle spray	desoximetasone, topical spray	vehicle spray
ITT [(1)] Subjects	59	60	60	60
Age				
18-65	18/50 (36.0%)	2/44 (4.6%)	26/52 (50.0%)	7/45 (15.6%)
>65	5/9 (55.6%)	2/16 (12.5%)	6/8 (75.0%)	3/15 (20.0%)
Sex				
Female	8/17 (47.1%)	1/17 (5.9%)	10/23 (43.5%)	3/25 (12.0%)
Male	15/42 (35.7%)	3/43 (7.0%)	22/37 (59.5%)	7/35 (20.0%)
Race				
Asian	-	0/1 (0%)	-	0/2 (0%)
Black	1/2 (50%)	0/2 (0%)	1/2 (50%)	-
White	22/57 (38.6%)	4/57 (7.0%)	30/57 (52.6%)	10/56 (17.9%)
Native American	0-	-0	0-	0/1 (0%)
Other Pacific	0-	-0	1/1 (100%)	0/1 (0%)

Source: Biostatistical Review by Carin Kim, Ph.D., Table 14

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant established the optimal dosing regimen (concentration, duration of application and dosing interval) with data from trial DSXS -0906. This was a Phase 2, double-blind, vehicle-controlled, randomized, dose ranging, multicenter trial which evaluated the efficacy and safety of 2 concentrations of desoximetasone topical spray (0.05% and 0.25%) in 151 subjects with moderate to severe psoriasis. (Refer to Section 5.3. for a review of Protocol Number: DSXS -0906 and Table 14 for the results of the trial.) The only treatment group to achieve statistically significant clinical success compared to vehicle applied desoximetasone topical spray, 0.25% twice daily for 28 days.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The applicant did not design any trials in the development program to assess persistence of effect or tolerance of effect.

6.1.10 Additional Efficacy Issues/Analyses

Efficacy results appear to be consistent across study sites as illustrated below. Refer to Figure 1: Efficacy by Center Plots

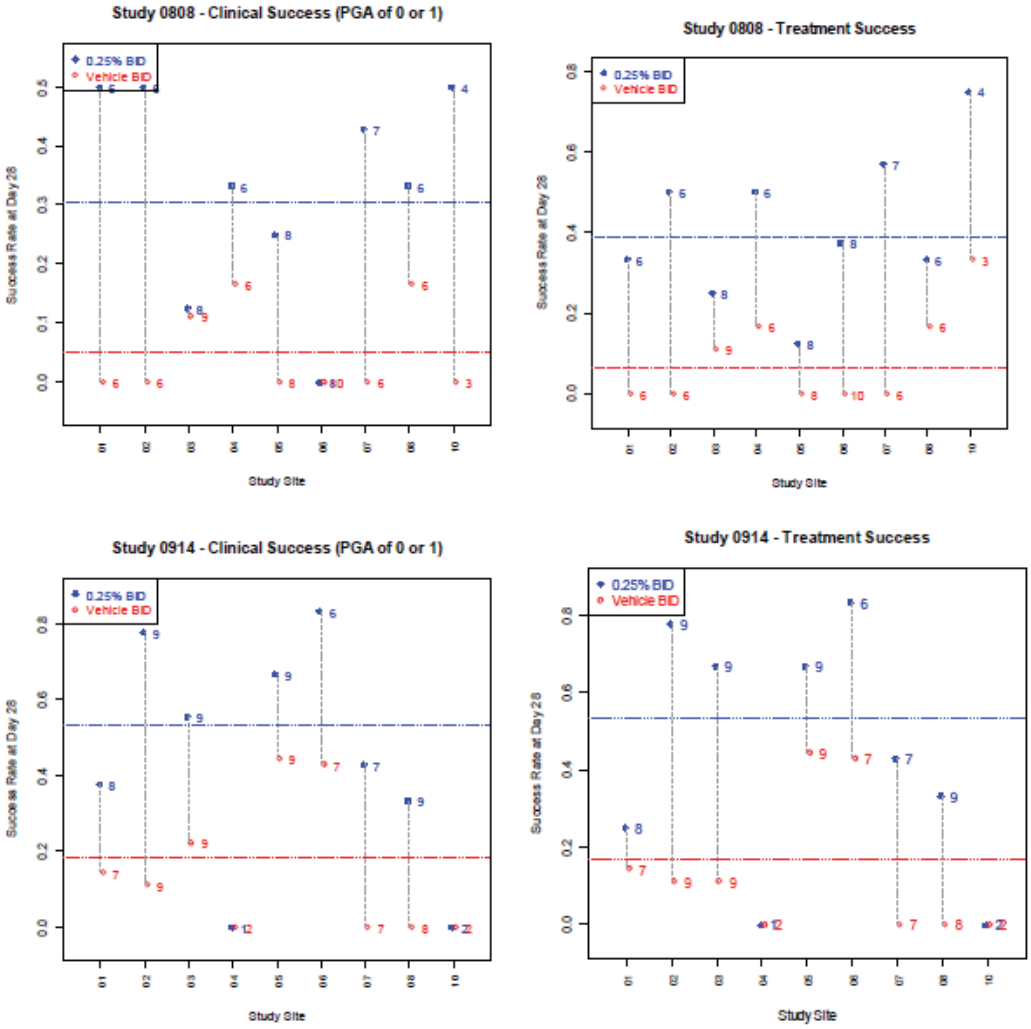

Figure 1: Efficacy by Center Plots

Source: Biostatistical Review by Carin Kim, Ph.D.

The statistical reviewer conducted an analysis of efficacy based on overall disease severity at Baseline (PGA and %BSA) and target lesion severity at Baseline (erythema, scaling and plaque elevation). However, the number of subjects in each category was too small to allow a reasonable inference.

7 Review of Safety

Safety Summary

The applicant submitted safety data from eight clinical trials in the marketing application for desoximetasone topical spray, 0.25% for the treatment of plaque psoriasis in patients 18 years and older. This reviewer evaluated safety data from two Phase 3 trials (DSXS-0808 and DSXS-0914) enrolling 240 subjects, a dose range finding Phase 2 trial

(DSXS-0906) enrolling 151 subjects, a vasoconstriction trial enrolling 32 subjects (10715005), an HPA axis suppression trial (DSXS-0805) enrolling 24 subjects, a phototoxicity trial (DSXS-0904) enrolling 38 subjects, a photoallergenicity trial enrolling 58 subjects and an irritation/sensitization trial enrolling 297 subjects.

The safety population consisted of a total of 284 subjects age 18 years and above with moderate to severe plaque psoriasis who participated in the three multicenter, vehicle-controlled trials (DSXS-0808, DSXS-0914 and DSXS-0906) and were exposed to desoximetasone topical spray or vehicle spray applied twice per day for 28 days. A total of 149 subjects applied desoximetasone topical spray 0.25% twice per day and 135 subjects applied vehicle spray twice per day. All enrolled subjects had a definitive diagnosis of stable plaque psoriasis involving ≥10% BSA with a total lesion severity score (TLSS) of ≥7 for the target lesion, and a Physician Global Assessment (PGA) score of 3 (moderate), 4 (moderately severe) or 5 (severe) at Baseline. Subjects with psoriasis of the scalp/face requiring treatment during the trial were excluded.

Data collected from subjects in the intent to treat analysis set served as the basis for the safety evaluation. The overall exposure to the study product was adequate to characterize the safety profile in the intended population (age 18 years old and above). The safety assessments included adverse events elicited by active query and open ended questioning (summarized by severity, frequency and relationship to the study drug), vital signs, and laboratory tests (e.g. pregnancy testing in all female subjects of child bearing potential.)

There were no deaths or non-fatal serious adverse events (SAEs) among subjects in the development program. Three subjects (3/284, 1%) in the safety population reported adverse events determined to be severe in intensity. All 3 subjects were enrolled in trial DSXS-0808 and review of the Case Report Forms indicates that these severe AEs are likely to be related to the study product. Two subjects who were enrolled in the desoximetasone topical spray, 0.25% treatment group reported severe pruritus at the application site (1 subject) and ulceration (1 subject). One subject who was enrolled in the vehicle spray treatment group, reported severe redness on her legs at the application site.

The incidence of adverse events in the safety population resulting in subject discontinuation was 0.8% in the desoximetasone topical spray 0.25% day treatment group and 3.0% in the vehicle spray treatment group. Among the 284 subjects in the safety population a total of 5 subjects withdrew from the trials (trial DSXS-0808, trial DSXS-0914 and trial DSXS-0906) due to treatment emergent adverse events. One subject who applied desoximetasone topical spray reported application site pruritus and psoriasis which led to discontinuation from the trial. Four subjects who applied vehicle spray reported application site burning (1 subject), application site dryness and itching (1 subject), application site erythema (1 subject), and application site stinging and worsening of psoriasis (1 subject) which led to discontinuation from the trials.

Among the subjects in the safety population, at least one adverse event (AE) was reported by 20% of subjects in the desoximetasone topical spray treatment group and 28% of subjects in the vehicle spray treatment group. The most common adverse reactions (≥1%) in subjects exposed to desoximetasone topical spray included: application site dryness (2.7%), application site irritation (2.7%), and application site pruritus (2.0%). However, the incidence of these reactions was greater in the vehicle spray group than the desoximetasone topical spray group (0.25% twice per day).

Analysis of adverse events by age (≤65 versus >65) and race (White versus Non-white) was cofounded by the limited numbers of subjects > 65 years old and Non-white subjects.

The applicant submitted additional safety data from 5 clinical trials which assessed vasoconstriction (10715005), HPA axis suppression (DSXS-0805) and dermal safety (DSXS-0804, DSXS-0904, DSXS-0905). The applicant presented the safety data from these 5 clinical trials separately due to differences in trial design, study population and extent of exposure to the study product. There were no deaths and no serious adverse events (SAEs). One pregnancy occurred in a 22 year old subject enrolled in trial DSXS-0804 (irritation and sensitization) on Day 36. The subject refused confirmatory serum pregnancy testing and reported a “spontaneous abortion” 7 days after the positive pregnancy test.

The majority of the subjects who enrolled in one of the 5 clinical trials providing additional safety data completed the trial. The most common reason for discontinuation was “withdrawal by subject.” Six subjects withdrew from 2 trials due to adverse events. In Trial DXSX 0804 (irritation and sensitization), 4 subjects withdrew due to adverse events (AEs). The AEs reported for this trial were: pharyngitis; hypertension; bilateral hand rash/ generalized itching; abdominal pain/ nausea/ vomiting/ loose stools/ elevated pulse. In Trial DXSX 0905 (photoallergenicity), 2 subjects withdrew due to adverse events (AEs). The AEs reported for this trial were herpes viral infection and back pain from herniated disc. Examination of the Case Report Forms indicates that the only adverse event that was probably related to the study treatment was the report of bilateral hand rash associated with generalized pruritus.

Subjects experienced adverse events in Trial DSXS-0905 (photoallergenicity), DSXS-0805 (HPA Axis suppression) and Trial DSXS-0804 (irritation and sensitization).There were no adverse events reported among healthy subjects enrolled in Trial 10715005, (vasoconstriction) and Trial DSXS-0904 (phototoxicity). In Trial DSXS-0905, 6 healthy subjects (10%) reported adverse events. The only adverse event reported by more than 1 subject was nasopharyngitis (2 subjects). Among the 24 subjects with plaque psoriasis enrolled in Trial DSXS-0805, 7 (29%) experienced treatment emergent adverse events and, no adverse event was reported by more than 1 subject except HPA suppression (5 subjects using applicant criteria and 3 using the FDA criteria). Among the 297 subjects enrolled in Trial DSXS-0804 (photosensitivity) there were 469 adverse

Reference ID: 3252617

events were reported in 180 subjects. Most of the adverse events resolved spontaneously prior to the end of treatment and were characterized as mild (99.6%).

The applicant conducted trial DSXS-0805 in adult subjects with a diagnosis of moderate to severe plaque psoriasis to provide data regarding systemic exposure and effect of desoximetasone topical spray 0.25% on the hypothalamic-pituitary axis. Twenty-one subjects had evaluable serum cortisol levels and the proportion of subjects demonstrating HPA axis suppression was 8.3% (1/12) in subjects having involvement of 10-15% of BSA, and 22.2% (2 / 9) in subjects having involvement of > 15% of their BSA. HPA axis suppression was defined as serum cortisol level ≤18 mcg/dL 30-min post cosyntropin stimulation.

The applicant conducted 3 provocative dermal safety trials in healthy adult subjects with the to-be-marketed formulation to establish the safety of desoximetasone topical spray. These trials evaluated the potential for irritation and sensitization (DSXS-0804), phototoxicity (DSXS-0904) and photoallergenicity (DSXS-0905). No subjects experienced significant irritation, sensitization, phototoxicity, or photoallergenicity under these trial conditions.

In conclusion, the safety database was reviewed and the following will be included in labeling:

> Adverse reactions that occurred in ≥ 1% of subjects treated with Topicort Topical Spray were application site dryness (2.7%), application site irritation (2.7%) and application site pruritus (2.0%).
>
> Another less common adverse reaction (<1% but >0.1%) was folliculitis.

7.1 Methods

The applicant submitted the following data which is summarized in Table 23 to support the safety of desoximetasone topical spray for the treatment of moderate to severe plaque psoriasis in subjects 18 years of age or older. This data includes safety information from 8 clinical trials, postmarketing adverse event reports, current labeling for desoximetasone products and results from a search of the world wide literature. Refer to Section 7.5 for a discussion of the results of the postmarketing adverse event reports and the search of the world wide literature.

This safety analysis is based on data from subjects enrolled in the Phase 3 trials DSXS-0808 and DSXS-0914 and the Phase 2 trial DSXS-0906 who were exposed to desoximetasone topical spray 0.25% or vehicle spray applied twice daily for 28 days.

Data from the special safety studies is discussed in Section 7.4.5 of this review. These trials were evaluated separately due to differences in study populating, treatment duration and dosing regimen. The following trials are summarized in Section 7.4.5 of this review:

Reference ID: 3252617

- 10715005: vasoconstriction in healthy subjects
- DSXS-0805: HPA axis suppression in subjects with psoriasis
- DSXS-0804: Irritation and Sensitization in healthy subjects
- DSXS-0904: Phototoxicity in healthy subjects
- DSXS-0905: Photoallergenicity in healthy subjects

Table 23: Sources of Safety Data for Desoximetasone topical spray, 0.25%

Source	Population	N Exposed (DSXS)	Study Design (or Data Source if not a Taro-sponsored study)
Taro-Sponsored Clinical Studies			
Pooled Studies (Phase 2 and 3 in Plaque Psoriasis)			
DSXS-0906	Adults (> 18 years) with stable moderate to severe plaque psoriasis involving ≥ 10% BSA	150[1] (120)	Double-blind, vehicle-controlled, randomized, parallel group, dose-ranging clinical study
DSXS-0808		120 (60)	Double-blind, vehicle-controlled, randomized, parallel design, clinical safety and efficacy study
DSXS-0914		120 (60)	Double-blind, vehicle-controlled, randomized, parallel design, clinical safety and efficacy study
Sub-total		*355[2] (205[2])*	
Clinical Pharmacology Studies			
Single Application			
10715005	Healthy adults	32 (32)	16-hour vasoconstriction study
DSXS-0904	Healthy adults	38 (38)	4-day phototoxicity study
Multiple Applications			
DSXS-0905	Healthy adults	58 (58)	6-week photo-allergenicity study (6 applications)
DSXS-0804	Healthy adults	297 (297)	5-week irritation/ sensitization study (9 applications)
DSXS-0805	Patients with moderate-to-severe plaque psoriasis involving ≥ 10% BSA	24 (24)	28-day HPA axis suppression study (53 applications)
Sub-total		*449 (449)*	
Total unique subjects[3]:		*791 (641)[3]*	
Medical Literature			
Published 2004 to 5 December 2011	--	--	One published case report (Donovan and DeKoven, 2006)
Postmarketing Safety Data			
U.S. Food and Drug Administration	Primarily U.S. but includes foreign reports	--	432 adverse event reports from 1977 (first approval) through 30 September 2011
Taro Pharmaceuticals	Primarily U.S.	--	Reports received since the cut-off date of last Annual Reports for all marketed products[4]: 14 reports
Labeling			
Topicort® cream, gel, and ointment (Taro Pharmaceuticals)	--	--	Current FDA-approved labeling (cream and gel, May 2011; 0.25% ointment, Oct 2010)

Source: NDA 20-4141 SD 11; Clinical Summary;Table 2.7.4:1, pg. 4

BSA=body surface area; HPA=hypothalamic-pituitary-adrenal
1 One patient, 0906-03-0051, randomized to vehicle was not dosed in the clinic and did not return for subsequent visits, thus is excluded from the safety population.
2 35 patients identified as participating in more than one Phase 2/3 study are counted once (see Section 2.7.4.2.2.1.1.1 for discussion).

3 13 patients participating in a clinical pharmacology study and a Phase 2/3 study are counted once (see Section 2.7.4.1.1.1 for discussion): 5 patients participated in the Phase 2 dose- ranging study DSXS-0906 and went on to enroll into clinical pharmacology study DSXS-0805 and 8 patients participated in clinical pharmacology study DSXS-0805 and went on to enroll into the Phase 3 study DSXS-0914.
4 The cut-off dates for the annual reports are as follows: Desoximetasone Oinment, 0.05% - 16 Jan 2011; Desoximetasone Ointment, 0.25% - 06 Jun 2011; Desoximetasone Gel, 0.05% - 13 Jul 2011; Desoximetasone Cream, 0.05% and 0.25% - 29 Nov 2011.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The applicant submitted safety data from 8 clinical trials which were conducted in support of the desoximetasone topical spray, 0.25% marketing application. The primary safety database for desoximetasone topical spray, 0.25% is comprised of data from two 28 day, vehicle-controlled Phase 3 trials (DSXS-0808 and DSXS-0914) which enrolled a total of 240 subjects with moderate to severe psoriasis and a 28-day,vehicle controlled, Phase 2 dose range finding trial (DSXS-0906) which enrolled a total of 151 subjects with moderate to severe psoriasis. All enrolled subjects had a definitive diagnosis of stable plaque psoriasis involving ≥10% BSA with a total lesion severity score (TLSS) of ≥7 for the target lesion, and a Physician Global Assessment (PGA) score of 3 (moderate), 4 (moderately severe) or 5 (severe) at Baseline. Subjects with psoriasis of the scalp/face requiring treatment during the trial were excluded. Among the subjects enrolled in the Phase 2 trial (DSXS-0906), 44 subjects applied desoximetasone topical spray, 0.25% or vehicle spray twice per day for 28 days.

Table 24 includes a list of 36 subjects who participated in both the Phase 2 trial and one of the Phase 3 trials. The interval between the treatments administered to these subjects during the first and second trials was greater than 148 days. All subjects who participated in 2 trials met the enrollment criteria of both trials with regard to disease severity and percent BSA involvement with psoriasis.

The reviewer conducted a separate safety analysis of the data from 3 dermal safety trials (DSXS-0804, DSXS-0904, DSXS-0905) and 2 Clinical Pharmacology trials to evaluate vasoconstriction (10715005) and HPA axis suppression (DSXS-0805). Refer to Section 7.4.5 of this review.

7.1.2 Categorization of Adverse Events

All adverse events were coded on the basis of MedDRA version 12.1 terminology by system organ class and preferred term. The assignment of verbatim terms to system organ classes and preferred terms appears to be acceptable.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety analysis set included 240 subjects enrolled in the 2 Phase 3 Trials (DSXS-0808 and DSXS-0914) and the 44 subjects enrolled in the Phase 2 trial (DSXS-0906) who were randomized to receive treatment with desoximetasone topical spray 0.25% or vehicle spray twice daily for 28 days.

There were 36 subjects* who participated in the Phase 2 trial and one of the Phase 3 trials. The subject numbers are listed in Table 24. Twelve of these subjects were exposed to desoximetasone topical spray *twice per day* or vehicle spray *twice per day* in both trials.

Table 24: Subjects Enrolled in Both Phase 2 Trial DSXS-0906 and Phase 3 Trials DSXS-0808 or DSXS-0914

	Phase 3 Trial Treatment	Initial Phase 2 Treatment	Patient ID Phase2/Phase 3	Days Between Treatments
DSXS-0808	Desoximetasone 0.25% BID	Desoximetasone 0.25% BID	02-018/07-118	273
			02-025/07-120	224
			02-027/07-114	197
			04-142/05-154	274
		Vehicle BID	04-158/05-143	257
		Lower doses	01-092/01-001	245
			01-126/01-008	233
			01-275/01-004	185
			02-012/07-123	287
			02-017/07121	277
			02-021/07-116	221
			02-024/07-112	218
			04-146/05-150	267
			04-264/05-145	231
			07-072/06-032	272
			07-079/06-024	202
			07-081/06-025	197
			07-087/06-028	195
		Vehicle QD	01-097/01-005	248
			04-150/05-148	267
	Vehicle BID	Desoximetasone 0.25% BID	01-098/01-002	230
			02-016/07-111	270
			04-284/05-147	148
			04-267/05-146	226
		Vehicle BID	01-091/01-003	245

			02-011/07-119 07-074/06-026	273 236
		Lower doses	02-020/07-113 02-026/07-122 04-157/05-144 04-262/05-153 04-269/05-149 07-071/06-023	218 228 260 238 226 239
		Vehicle QD		
DSXS-0914	DSXS-0808	Lower doses	03-056/02-058	180
	Vehicle BID	Lower doses	03-049/02-138	302

* The applicant identified 35 subjects who participated in the Phase 2 trial and one of the Phase 3 trials. During the course of the safety evaluation this reviewer identified and confirmed that an additional subject participated in more than one trial.
Source: Modified from NDA 20-4141; SD-11, Clinical Summary, Table 2.7.4:7 pg. 14

The safety data from the 5 special studies is discussed separately due to differences in trial design and study population. Refer to Section 7.4.5 of this review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall Exposure

Overall exposure to the study product during the Phase 2 and Phase 3 trials is displayed in the following tables (Table 25 and Table 26) in terms of dosing regimen and duration of treatment. During each trial, study site personnel dispensed a total of 200 ml of study product to each subject. Investigators did not record the amount of study product used per day or the number of applications per subject per day (the total number of applications per subject is recorded on the CRF. Among the subjects included in the primary safety database, 135 subjects applied vehicle spray twice per day and 149 subjects applied desoximetasone topical spray, 025% twice per day. The majority of subjects who applied desoximetasone topical spray, 025% twice per day were exposed to the study product for 27 to 31 days (86.6%).

Table 25 includes the number of subjects who were exposed to each formulation and dosing regimen in the Phase 2 and Phase 3 trials. Table 26 includes the duration of exposure categorized by treatment group in the pooled safety population. The duration of exposure was similar across treatment groups.

Table 25: Number of Subjects Exposed to Each Dosing Regimen during the Phase 2 and Phase 3 Trials

Study No.	Planned Treatment	Pooled Treatment Groups			Total Active
		0.25% *b.i.d.* (N=149)	<0.25% *b.i.d.* (N=91)	Vehicle (N=150)	
DSXS-0906	DSXS 0.05% *q.d.*	--	30	--	30
	DSXS 0.05% *b.i.d.*	--	31	--	31
	DSXS 0.25% *q.d.*	--	30	--	30
	DSXS 0.25% *b.i.d.*	29	--	--	29
	Vehicle *q.d.*	--	--	15	--
	Vehicle *b.i.d.*	--	--	15	--
DSXS-0808	DSXS 0.25% *b.i.d.*	60	--	--	60
	Vehicle *b.i.d.*	--	--	60	--
DSXS-0914	DSXS 0.25% *b.i.d.*	60	--	--	60
	Vehicle *b.i.d.*	--	--	60	--

Source: NDA 20-4141; Integrated Summary of Safety Table 17 pg. 41
Phase 2: DSXS-906
Phase 3: DSXS-0808; DSXS-0914

Table 26: Duration of Exposure: Desoximetasone versus Vehicle -Pooled Safety Population

Characteristic	Statistic or Category	Pooled Treatment Group	
		desoximetasone spray 0.25% twice per day N=149	vehicle spray twice per day N=135
Duration (days)	Mean ±SD	27.7± 4.3	27.7 ±4.9
	Median (Range)	29 (1-40)	29 (8-36)
Duration of Exposure Category (days)	$1 \leq 9$	2 (1.3%)	6 (4.4%)
	$10 \leq 17$	5 (3.4%)	2 (1.5%)
	$18 \leq 26$	11 (7.4%)	7 (5.2%)
	$27 \leq 31$	129 (86.6 %)	117 (86.0%)
	Exposure > 31	2 (1.3 %)	3 (2.2%)

Source: Modified from NDA 204141 SD 11; Clinical Summary, Table 2.7.4:12, pg.18

Demographics of Target Population

The baseline demographic information regarding subjects enrolled in Trial DSXS-0906, Trial DSXS-0808 and Trial DSXS-0914 is pooled by treatment group and presented in Table 27.

The key demographic characteristics of subjects who were randomized to receive treatment with desoximetasone topical spray 0.25% or vehicle spray twice daily for 28 days are comparable. The majority of the subjects in the safety population are White, male, not Hispanic/Latino and approximately 50 years of age. Subjects in the vehicle

group who applied the study product twice per day had slightly greater height, weight and BSA than subjects in the desoximetasone 0.25% group who applied the study product twice per day.

Table 27: Summary of Baseline Characteristics – Pooled Safety Population and Other Treatment Groups

Characteristic	Statistic or Category	Pooled Treatment Groups				Total Active (N=219)
		DSXS		Vehicle		
		0.25% *b.i.d.* (N=128)	<0.25% *b.i.d.* (N=91)	*q.d.* (N=15)	*b.i.d* (N=121)	
Age (years)	Mean ± SD	48.9 ± 14.5	50.0 ± 14.0	53.5 ± 12.9	52.1 ± 15.0	49.4 ± 14.3
	Median	50	50	59	52	50
	Range	19 - 81	22 - 82	25 - 73	20 - 81	19 - 82
Sex	Female	48 (37.5%)	39 (42.9%)	1 (6.7%)	43 (35.5%)	87 (39.7%)
	Male	80 (62.5%)	52 (57.1%)	14 (93.3%)	78 (64.5%)	132 (60.3%)
Race	White	122 (95.3%)	84 (92.3%)	15 (100%)	112 (92.6%)	206 (94.1%)
	African American	5 (3.9%)	5 (5.5%)	0	2 (1.7%)	10 (4.6%)
	Other†	1 (0.8%)	2 (2.2%)	0	7 (5.8%)	3 (1.4%)
Ethnicity	Hispanic or Latino	26 (20.3%)	28 (30.8%)	4 (26.7%)	17 (14.0%)	54 (24.7%)
	Not Hispanic or Latino	102 (79.7%)	63 (69.2%)	11 (73.3%)	104 (92.6%)	165 (75.3%)
Height (cm)	Mean ± SD	170.9 ± 10.0	171.1 ± 14.2	174.0 ± 6.4	173.4 ± 17.2	171.0 ± 11.9
	Median	171	173	173	173	171
	Range	140 – 193	83 – 193[1]	165 – 188	143 – 318	83 – 193
Weight (kg)	Mean ± SD	91.5 ± 21.80	92.4 ± 24.34	104.9 ± 25.23	95.2 ± 27.10	91.9 ± 22.84
	Median	88.0	88.0	101.0	92.0	88.0
	Range	51.5 – 162.0	11.5 – 153.5[1]	71.0 – 164.0	30.0-218.0	11.5 – 162.0
BSA (m^2)	Mean ± SD	2.072 ± 0.268	2.102 ± 0.293	2.235 ± 0.262	2.118 ± 0.316	2.084 ± 0.279
	Median	2.04	2.09	2.23	2.10	2.04
	Range	1.53 – 2.79	1.57 – 2.80	1.80 – 2.78	1.40 – 3.30	1.53 – 2.80

Source: NDA 20-4141 SD 11; Clinical Summary, Table 2.7.4:8 pg.15
* These demographic and other baseline characteristics do not double-count the subjects who participated in two trials (Phase 2 and Phase 3). For the purpose of this table, these subjects are counted only once in their trial of first participation.
**Other includes American Indian, Alaskan Native, Asian; Native American/White, Native Hawaiian or other Pacific Islander.

7.2.2 Explorations for Dose Response

Trial DSXS-0906 explored two dosing regimens (once versus twice daily) and two doses of desoximetasone topical spray (0.05% and 0.25%). A total of 151 subjects were randomly assigned to one of 6 treatment groups and applied the study product gently to all affected areas once or twice per day for 28 days. Refer to Section 5.3 for a review of the protocol.

The only treatment group to achieve statistically significant clinical success (PGA score of 0 or 1) and treatment success (target lesion score of 0 or 1 for erythema, scaling and plaque elevation) applied desoximetasone topical spray 0.25% twice daily. The

treatment group who applied desoximetasone topical spray, 0.25% once daily achieved statistically significant treatment success only.

In Trial DSXS-0906 there were no unexpected adverse events, significant differences in the frequency of adverse events between the treatment groups and no dose dependent adverse events. Application site dryness and headache were the only adverse events reported in this trial by more than one subject in any treatment group.

7.2.3 Special Animal and/or In Vitro Testing

The applicant conducted no special animal studies or in vitro testing.

7.2.4 Routine Clinical Testing

The laboratory evaluation during the Phase 3 trials (DSXS-0808 and DSXS-0914) and the Phase 2 dose range finding trial (DSXS-0906) consisted of urine pregnancy testing which was conducted at Baseline and at Day 28. The applicant reported no pregnancies during the course of these Phase 2 and Phase 3 trials. However, a 22 year old woman enrolled in trial DSXS-0804 (irritation and sensitization) with a negative pregnancy test on Day 1 had a positive pregnancy test on Day 36. The subject refused confirmatory pregnancy testing and stated her intention to terminate the pregnancy. She reported a spontaneous abortion 7 days after the positive pregnancy test but provided no additional information.

7.2.5 Metabolic, Clearance, and Interaction Workup

During trial DSXS-0805, investigators collected samples to assess plasma desoximetasone concentration at Baseline, Day 14 and Day 28 at unspecified timepoints. The applicant stated that subjects with greater cutaneous involvement with psoriasis had greater plasma concentrations of desoximetasone. However, in the absence of a full PK profile, no definitive conclusion may be drawn.(Clinical Pharmacology Review dated 1/18/2013).

An evaluation of potential drug interactions was not included in this submission. Clinically meaningful drug interactions were not expected based on the limited systemic exposure demonstrated in the bioavailability trials. Current approved labeling for other topical desoximetasone formulations does not contain data regarding drug interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The primary systemic safety assessment for topical corticosteroids is Cosyntropin Stimulation Testing (CST) to evaluate HPA suppression (Trial DSXS-0805). Investigators administered 0.125 mg of Cortrosyn® by intramuscular injection to 24 subjects with moderate (10-15% BSA affected) or severe (>15% BSA affected) psoriasis. CST was conducted at Baseline and Day 28. An abnormal HPA response was defined as a 30-minute post stimulation serum cortisol level < 18 micrograms/dL. Refer to Sections 4.4.2. and 7.5 of this review and the Clinical Pharmacology Review dated 1/18/2013 for a discussion of these results.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during the course of these Phase 2 and Phase 3 trials.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events reported during the course of these Phase 2 and Phase 3 trials.

7.3.3 Dropouts and/or Discontinuations

The disposition of subjects in the pooled safety population (exposed to twice daily dosing with desoximetasone topical spray 0.25% or vehicle spray) is presented in Table 28. Greater than 90% of subjects in each treatment group from the pooled safety population completed the trials. The most common reasons for withdrawal from the desoximetasone topical spray, 0.25% treatment group were lack of efficacy, lost to follow-up and other reasons. The most common reasons for withdrawal from the vehicle spray treatment group were adverse events including exacerbation of psoriasis and other reasons.

Table 28: Summary of Disposition and Reasons for Discontinuation-Pooled Safety Population

	Pooled Treatment Groups	
	desoximetasone spray 0.25% twice per day	vehicle spray twice per day
Total (N)	149	135
Completed	137 (91.9%)	122 (90.4%)
Discontined	12 (8.1%)	13 (9.6%)

Lost to Follow-up	2 (1.3%)	1 (0.74%)
Lack of Efficacy	2 (1.3%)	1 (0.74%)
Withdrawal by subject	1 (0.75)	3(2.2%)
Adverse event (worsening psoriasis)	1 (0.75)	3(2.2%)
Adverse event (other)	0	1 (0.74%)
Enrollment in error	0	1 (0.74%)
Other	6 (4.0%)	3 (2.2%)

Source: Modified from NDA 204141, SD11, Clinical Summary, Table 2.7.4:13 pg. 19
Other reasons were:

- Desoximetasone: ran out of medication, (0808-03-176; 0808-03-178; 0906-05-172), early out of window (0914-03-059; 0914-10-152), subject schedule (0914-01-028);
- Vehicle: early visit outside of window (0914-10-151; 0914 10-153) , subject schedule (0914-01-027)

A total of 5 subjects withdrew from their Phase 2 or Phase 3 Trials in the pooled safety population due to treatment emergent adverse events. A 70-year-old white male (0808-03-053) who applied desoximetasone topical spray 0.25% twice per day, reported application site pruritus on Day 13 and withdrew from the trial. Refer to Section 7.3.4 for a brief narrative of this adverse event. Four subjects who applied vehicle spray twice per day, withdrew from their trials in the pooled safety population and the following brief narratives from the Case Report Forms summarize the adverse events.

1. 0808-01-007
   A 35 year old white female with a history of plaque psoriasis since 1991, obesity, hypertension, hypertriglyceridemia and migraine headache complained of moderate worsening of skin dryness and itching. These symptoms were treated with Eucerin lotion and the study product was discontinued after 5 doses of treatment.

2. 0808-07-113
   A 75-year old white female, developed severe redness on her legs, the site of application of study drug (application site erythema) on Day 4. The event was judged possibly related to treatment and the drug was withdrawn on Day 8. The event resolved by Day 13. This subject was exposed to desoximetsone 0.05% in the Phase 2 trial DSXS-0906 and then participated in Phase 3 trial DSXS-0808.

3. 0914-02-053
   A 25 year old white female with a history of plaque psoriasis since 2007, asthma and sciatica experienced moderate stinging of the application site and worsening of psoriasis with resultant pain and insomnia. The study drug was discontinued after 14 doses of treatment. Her medications at Baseline were albuterol, ibuprofen and Mirena.

4. 0914-04-075

A 54 year old white female with a history of plaque psoriasis since 1970, amputation of her right arm, asthma, brain aneurism, knee replacement, gastric bypass (reversed), knee pain and hysterectomy experienced moderate burning after 14 doses of treatment. The study drug was discontinued. Her medications at Baseline were hydrocodone and Lyrica.

7.3.4 Significant Adverse Events

Among the 284 subjects in the primary safety database, three subjects reported adverse events that were assessed as severe in intensity (application site pruritus, cutaneous ulcer, application site redness). All 3 subjects were enrolled in trial DSXS-0808 and the adverse events were likely to be related to the study drug according to the data included on the case report forms. Two subjects were enrolled in the desoximetasone topical spray, 0.25% treatment group and one subject was enrolled in the vehicle spray treatment group. The following brief narratives from the Case Report Forms provide a description of these subjects and the adverse events:

Desoximetasone topical spray, 0.25% twice per day treatment group

1. 0808-03-053
   A 70 year old white male with a history of plaque psoriasis since 2007 complained of severe itching at the application site on Day 13 and observed the onset of additional plaques of psoriasis on Day 15. Investigators did not assess these 2 events as serious but the study drug was discontinued on Day 15.

2. 0808-08-137
   A 61 year old white male with a history of plaque psoriasis since 2007, obesity, arthritis, and left tibial fracture developed hypertension on Day 14 and a cutaneous ulcer adjacent to his right patella on Day 23. Although the ulcer was not localized to the application site, investigators assessed the adverse event to be severe and possibly related to the study drug. He was treated with lisinopril (hypertension), Bactrim DS and Ceftriaxone (ulcer). His medications at Baseline included Diclofenac. The subject completed the trial but continued to report the presence of an ulcer at follow-up on Day 31.

Vehicle spray twice per day treatment group

3. 0808-07-113
   A 75 year old white female with a history of plaque psoriasis since 1996, hypothyroidism and hypercholesterolemia reported severe redness on her legs at the application site. Her baseline medications included an 81 mg aspirin, simvastatin, levothyroxine and Eucerin Lotion. The redness was treated with Eucerin Lotion and the study drug was discontinued on Day 4.

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7.3.5 Submission Specific Primary Safety Concerns

The primary safety concern regarding topical corticosteroids is HPA axis suppression which is discussed in Section 7.2.6 and 7.4.5 of this review.

Based on extensive data regarding this moiety, the applicant evaluated local and systemic safety adequately.

7.4 Supportive Safety Results

Refer to Sections 7.4.5 and 7.5 of this review.

7.4.1 Common Adverse Events/Adverse Reactions

Adverse Events

Treatment emergent adverse events (TEAE) observed in ≥ 1% of subjects in each treatment group are presented in Table 29 . The most common TEAEs in both treatment groups involved the application site (7.4% in desoximetasone topical spray group versus 13.3% in the vehicle spray group) and skin/subcutaneous tissue (4.0% in desoximetasone topical spray group versus 2.9% in the vehicle spray group).

The most common systemic adverse events were diarrhea (1.3% in desoximetasone topical spray group versus 1.5% in the vehicle spray group) and headache (2.7% in desoximetasone topical spray group versus 2.2% in the vehicle spray group). Although headache, hypertension and arthralgia were reported in ≥ 1% of subjects in the desoximetasone treatment group and with greater frequency in the desoximetasone topical spray group than the vehicle spray group, data included in the Case Report Forms (CRF) does not offer substantial support that these adverse events are related to treatment.

The adverse event of headache was transient (resolved within one day) in all subjects and required no treatment or OTC treatment. The two subjects who experienced multiple headaches had other co-morbidities (e.g. hypertension and seasonal allergies) which may have contributed to the development of this adverse event.

As discussed in Section 7.4.3 all subjects who experienced TEAE associated with elevated blood pressure had a blood pressure measurement above the normal range at baseline.

Among the 8 subjects who reported adverse events related to musculoskeletal and connective tissue disorders, 2 subjects reported psoriatic arthritis at baseline, one subject reported wrist pain at baseline and one reported fibromyalgia at baseline. Although shoulder pain was the most common musculosketetal complaint (4 subjects), all cases resolved during the trial and the maximum duration was 5 days. Furthermore, the evaluation of musculosketetal AEs may be confounded by undiagnosed underlying

psoriatic arthritis of the axial or peripheral skeletal system which is characterized by pain, joint swelling and stiffness.[3]

Although 2 subjects experienced folliculitis, only 1 subject observed the eruption at the application site. Thus, review of the data from the Case Report Forms (CRF) indicates that only one case of folliculitis is likely to be related to the application of desoximetasone topical spray {1/149 (0.7%)}.

Table 29: Number (%) of Subjects with at Least One TEAE Occurring in ≥ 1% of Subjects in Any Treatment Group-Pooled Safety Population

MedDRA System Organ Class MedDRA Preferred Term	Pooled Treatment Group	
	desoximetasone topical spray 0.25% twice per day N=149	vehicle spray twice per day N=135
Number of Subjects with at Least One TEAE	29 (19.5%)	38 (28.1%)
Gastrointestinal Disorders	5 (3.4%)	5 (3.7%)
Diarrhea	2 (1.3%)	2 (1.5%)
General Disorders and Site Administration	11 (7.4%)	18 (13.3%)
Application site dryness	4 (2.7%)	7 (5.2%)
Application irritation	4 (2.7%)	5 (3.7%)
Application pruritus	3 (2.0%)	5 (3.7%)
Application erythema	0	2 (1.5%)
Application pain	0	2 (1.5%)
Infections and Infestations	1 (0.7%)	2 (1.5%)
Furuncle	0	0
Tooth Infection	0	0
Musculoskeletal and Connective Tissue Disorders	4 (2.7%)	4 (3.0%)
Arthralgia	2 (1.3%)	1 (0.7%)
Back Pain	0	1 (0.7%)
Musculoskeletal Pain	2 (1.3%)	1 (0.7%)
Nervous System Disorders	4 (2.7%)	7 (5.2%)
Headache	4 (2.7%)	3 (2.2%)
Respiratory, Thoracic, and Mediastinal Disorders	2 (1.3%)	6 (4.4%)
Nasopharyngitis	1 (0.7%)	2 (1.5%)
Upper Respiratory Tract Infection	0	2 (1.5%)

3 LC Coates, Conaghan PG, Emery P et al. Sensitivity and Specificity of the Classificaiton of Psoriatic Arthritis Criteria in Early Psoriatic Arthritis. Arthritis& Rheumatism. Vol 64, No 10, October 2012, pp.3150-3155.

Skin and Subcutaneous Disorders	6 (4.0%)	3 (2.2%)
Excoriation	0	0
Folliculitis*	2 (1.3%)	0
Psoriasis	1 (0.7%)	2 (1.5%)
Rash	0	0
Vascular Disorders	2 (1.3%)	1 (0.7%)
Hypertension	2 (1.3%)	1 (0.7%)

Source: NDA 204141, SD11: Section 2.7 Clinical Summary, pg. 25.
*Per the CRF one case of folliculitis was unrelated to treatment.

Thirty eight subjects (32%) reported a total of 69 adverse events in Trial DSXS-0808 compared to 21 subjects (18%) who reported a total of 34 adverse events in Trial DSXS-0914. Application site dryness was the most common adverse event among subjects treated with desoximetasone topical spray 0.25% in Trial DSXS-0808 while application site irritation was the most common adverse event among subjects treated with desoximetasone topical spray in Trial DSXS-0914.

Adverse Reactions

Adverse reactions occurring in ≥1% of subjects in the pooled safety population are presented in Table 30. The most common adverse reactions observed with the use of the proposed drug product were application site dryness, application site irritation and application site pruritus. These reactions were reported with greater frequency in the vehicle spray treatment group than in the desoximetasone topical spray, 0.25% treatment group.

Table 30: Number (%) of Subjects with Adverse Reactions Occurring in ≥1% of Subjects in the Safety Population

	Pooled Treatment Group	
	desoximetasone topical spray 0.25% twice per day N=149	vehicle spray twice per day N=135
Number of Subjects with Adverse Reactions*	13 (8.7%)	18 (13.3%)
General Disorders and Site Administration	11 (7.4%)	18 (13.3%)
Application site dryness	4 (2.7%)	7 (5.2%)
Application irritation	4 (2.7%)	5 (3.7%)
Application pruritus	3 (2.0%)	5 (3.7%)
Application erythema	0	2 (1.5%)
Application pain	0	2 (1.5%)

*Related (possible, probable, definite) TEAE
Source: NDA 204141, SD 11, Table 2.7.4:18 Clinical Summary, pg. 29
Refer to Section 9.1 of this review for recommendations regarding labeling.

7.4.2 Laboratory Findings

The only laboratory assessment performed as part of the safety evaluation during trial DSXS-0808, trial DSXS-0914 and trial DSXS-0906 was pregnancy testing. Refer to Section 7.2.4 of this review.

7.4.3 Vital Signs

Table 31 presents a summary of the changes in vital sign measurements from Baseline to the end of the trial from subjects included in the pooled safety population (DSXS-0808, trial DSXS-0914 and trial DSXS-0906) who applied the study product twice per day for 28 days. Individual vital sign measurements varied widely, although the mean changes were not significant.

Table 31: Summary of Changes in Vital Signs from Baseline to End of Treatment

Parameter	Statistic	0.25% BID	Vehicle BID
Systolic Blood Pressure mmHg	N	146	134
	Mean	0.5	-0.6
	SD	11/4	12.0
	Median	0	0
	Min/Max	-47/54	-45/43
Diastolic Blood Pressure mmHg	N	146	134
	Mean	0	-1.0
	SD	8.2	8.9
	Median	0	0
	Min/Max	-20/42	-42/29
Temperature (F)	N	146	134
	Mean	-0.02	0.03
	SD	0.60	0.59
	Median	0	0
	Min/Max	-1.7/1.9	-1.9/2.0
Pulse Rate (beats/min)	N	146	134
	Mean	1.1	1.3
	SD	8.8	9.2
	Median	0	2
	Min/Max	-27/32	-24/33
Respiratory Rate (breaths/min)	N	146	134
	Mean	-0.1	-0.1

	SD	2.3	2.1
	Median	0	0
	Min/Max	-8/10	-8/8

Source: NDA 204141 SD 19; Extended 14.10.3 Summary of Change in Vital Sign Measurements from Baseline to End of Study Pooled Safety Population
(Normal ranges for vital signs according the National Institutes of Health (Medline Plus) are:

- Blood pressure: 90/60 mm/Hg to 120/80 mm/Hg
- Breathing: 12 - 18 breaths per minute
- Pulse: 60 - 100 beats per minute
- Temperature: 97.8 - 99.1 degrees Fahrenheit / average 98.6 degrees Fahrenheit

Table 32: Subjects with TEAEs Associated with Elevated Blood Pressure

Patient No.	Age / Sex / Race	Adverse Event (Study Day)	Systolic / Diastolic Values (mmHg)	
			Baseline	End of Study
DSXS 0.25% *b.i.d.*				
0808-04-045	73 / F / C	Hypertension (30) [1]	148 / 88	175 / 101
0808-08-137	61 / M / C	Hypertension (10)	166 / 92	119 / 73
0914-05-044	40 / M / C	Blood Pressure Increased (29)	136 / 90	190 / 132
Vehicle				
0914-03-189	41 / F / C	Hypertension (6)	140 / 86	130 / 90

Source: NDA 204141 SD-11, Integrated Summary of Safety, Table 25, pg. 52
M = Male; F = Female; C = Caucasian
1 Patient had a previous history of hypertension (verbatim, 'exacerbation').

All subjects who experienced TEAE associated with elevated blood pressure had a blood pressure measurement above the normal range at baseline (Normal range: 90/60 mm/Hg to 120/80 mm/Hg according to the National Institutes of Health).

No subjects in the safety population experienced treatment emergent adverse events related to decreases in blood pressure or changes in pulse.

7.4.4 Electrocardiograms (ECGs)

The applicant requested a waiver from the need to conduct a clinical evaluation of the potential for desoximetasone topical spray, 0.25% to cause QT/QTc interval prolongation or proarrythmic effects as per the ICH E14 guidance (NDA 20-4141 SD - 004; 7/23/2012).
The applicant provided the following rationale for the waiver:

> "The primary basis for the waiver is the minimal systemic absorption of desoximetasone following topical application, even under conditions intended to maximize absorption. The reformulation does not result in increased exposure to desoximetasone relative to the approved products. As described below, concentrations are < 1 ng/mL, using sensitive assay methods. The lack of a proarrhythmic effect is supported by a nonclinical study (in which

desoximetasone was administered subcutaneously) and the extensive clinical experience with the approved topical formulations of desoximetasone."

The applicant provided the following supportive data:

- Pharmacokinetic data included in the approved labels for Topicort® Emollient Cream 0.25% and Topicort® Ointment 0.25% indicate that the plasma level of desoximetasone after an radio labeled dose applied for 24 hours with occlusion was less than 6 ng/mL.(Pharmacokinetic Section for labeling for Topicort® Emollient Cream 0.25% and Topicort® Ointment 0.25%.) In comparison, the plasma level of desoximetasone topical spray applied for 28 days to subjects with greater than 15% BSA affected with psoriasis was less than 1 ng/mL.

- ECGs following subcutaneous doses of desoximetasone (0.8 mg/kg/day) in Beagle dogs during a 6-month toxicity study (NDA 17-856) showed only rare T wave inversions (1 control, 1 low dose and 1 mid-dose) that were assessed as not treatment related.

- Although ECGs were not measured during any trials in this development program, there were no reports of adverse events related to the cardiovascular system. In addition, there were no reported adverse events pertaining to changes in ECG parameters in post-marketing data with desoximetasone or reports from the world wide literature pertaining to effects of desoximetasone on the QT interval.

The applicant provided sufficient justification for a waiver from the need to conduct a clinical evaluation of the potential for desoximetasone topical spray, 0.25% to cause QT/QTc interval prolongation or pro-arrhythmic effects.

7.4.5 Special Safety Studies/Clinical Trials

The applicant submitted additional safety data from 5 clinical trials which assessed vasoconstriction (10715005), HPA axis suppression (DSXS-0805) and dermal safety (DSXS-0804, DSXS-0904, DSXS-0905). Refer to Table 3 for a summary of these trials. Healthy adult volunteers participated in four trials (10715005, DSXS-0804, DSXS-0904, and DSXS-0905) and adult volunteers diagnosed with plaque psoriasis (at least 10% BSA) participated in the HPA axis suppression trial (DSXS-0805). Refer to Table 33 for demographic information regarding these subjects.

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Table 33: Summary of Demographics from Five Clinical Studies

Characteristic	Statistic or Category	Clinical Pharmacology Studies				
		10715005 (N=32)	DSXS-0904 (N=38)	DSXS-0905 (N=58)	DSXS-0804 (N=297)	DSXS-0805 (N=24)
Age (years)	Mean ± SD	25.1 ± 8.1	50.5 ± 11.9	47.6 ± 12.9	35.2 ± 11.9	52.1 ± 15.0‡ 46.8 ± 19.5†
	Median Range	21.0 18 – 47	52.1 23 – 70	48.1 20 – 71	34.0 18 – 67	-- 18 – 74
Sex	Female Male	29 (90.6%) 3 (9.4%)	35 (92.1%) 3 (7.9%)	45 (77.6%) 13 (22.4%)	170 (57.2%) 127 (42.8%)	12 (50.0%) 12 (50.0%)
Race	White African American	10 (31.3%) 20 (62.5%)	38 (100%) 0	57 (98.3%) 0	71 (23.9%) 174 (58.6%)	22 (91.7%) 2 (8.3%)
	Other*	2 (6.3%)	0	1 (1.7%)	52 (17.5%)	0
Ethnicity	Hispanic or Latino	3 (9.4%)	2 (5.3%)	4 (6.9%)	46 (15.5%)	6 (25.0%)
	Not Hispanic or Latino	29 (90.6%)	36 (94.7%)	54 (93.1%)	251 (84.5%)	18 (75.0%)

* Study 10715005: description not provided in report; Study DSXS-0905=Asian; Study DSXS-0804= American Indian or Alaska Native(4), Asian (5), Native Hawaiian or Other Pacific Islander (3), and undefined Other (40)
‡10-15% BSA affected by psoriasis
†>15% BSA affected by psoriasis
Source: NDA 204141, Integrated Summary of Safety, Table 4

Thirteen subjects who participated in the HPA axis suppression trial (DSXS-0805). participated in dose range finding Phase 2 Trial DSXS-0906 or Phase 3 Trial DSXS-0914. Eight subjects who participated in Trial DSXS-0805 later enrolled in Phase DSXS-0914. The interval between doses of study medication from the last dose in Trial DSXS-0805 to the first dose in Trial DSXS-0914 ranged from 99 to 160 days. Five subjects participated in Phase 2 Trial DSXS-0906 and later enrolled in Trial DSXS-0805. The interval between doses of study medications from the last dose in Trial DSXS-0906 to the first dose in Trial DSXS-0805 ranged from 35 to 71 days.

Based on the estimated half-life of desoximetasone (< 24 hours) and the rate of epidermal cell turnover, the drug product applied during the first trial should not impact the results of the second trial. In addition, all subjects who enrolled in a second trial met the inclusion criteria for disease severity for the second trial regardless of previous exposure to the study drug. (Clinical Pharmacologist, An-Chi Lu Ph.D.) Refer to Table 34.

Table 34: Subjects Enrolled in Phase 2 Trial DSXS-0906 or Phase 1 Trial DSXS-0805 Who Subsequently Enrolled in Phase 1 Trial DSXS-0805 or Phase 3 Trial DSXS-0914

First Study		N	Second Study		Patient IDs* 1st / 2nd Study (Days between treatment)
Study, Site	Treatment		Study, Site	Treatment	
DSXS-0906, Site 6	Vehicle	1	DSXS-0805 Site 1	DSXS 0.25% *b.i.d.*	06-200 / 01-101 (58)
	DSXS 0.25% *b.i.d.*	2			06-197 / 01-100 (49)
					06-203 / 01-103 (48)
	Lower doses	2			06-193 / 01-102 (71)
					06-208 / 01-108 (35)
DSXS-0805, Site 2	DSXS 0.25% *b.i.d.*	5	DSXS-0914 Site 2	Vehicle	02-207 / 02-055 (139)
					02-211 / 02-046 (101)
					02-220 / 02-048 (108)
					02-224 / 02-053 (99)
					02-226 / 02-142 (160)
		3		DSXS 0.25% *b.i.d.*	02-203 / 02-247 (136)
					02-213 / 02-054 (108)
					02-222 / 02-049 (107)

Source: NDA 204141Integrated Summary of Safety, Table 2
Phase 1 Trial DSXS-0805: HPA Axis Suppression Trial
Phase 2 Trial DSXS-0906: Dose Range Finding Trial
Phase 3 Trial DSXS-0914: Safety and Efficacy Trial

In contrast to the study population included in the Phase 2 and Phase 3 trials, the majority of subjects in the dermal safety, vasoconstriction and HPA Axis suppression trials were female and in Trial 10715005 (vasoconstriction) and Trial DXSX- 0804 (irritation and sensitization) the majority of subjects were African American. Enrolled subjects were generally healthy and used no medications except hormonal contraceptives within 7 days of initiation of study treatment.

The majority of the subjects who enrolled in one of the 5 clinical trials providing additional safety data completed the trial. The most common reason for discontinuation was “withdrawal by subject.” Six subjects withdrew from 2 trials due to adverse events. In Trial DXSX 0804 (irritation and sensitization), 4 subjects withdrew due to adverse events (AEs). The AEs reported for this trial were: pharyngitis; hypertension; bilateral hand rash/ generalized itching; abdominal pain/ nausea/ vomiting/ loose stools/ elevated pulse. In Trial DXSX 0905 (photoallergenicity), 2 subjects withdrew due to adverse events (AEs). The AEs reported for this trial were herpes viral infection and back pain from herniated disc. Examination of the Case Report Forms indicates that the only adverse event that was probably related to the study treatment was the report of bilateral hand rash associated with generalized pruritus.

The dermal safety, vasoconstriction and HPA Axis suppression trials are summarized in the following paragraphs and the types of safety data collected in each trial is outlined in Table 35.

Table 35: Safety Assessments Collected During the Dermal Safety, Vasoconstriction and HPA Axis Suppression Trials

Study Number	Primary Assessments	Additional Safety Data Collected		
		Adverse Events	Vital Signs	Clinical Laboratory Testing
Single Application				
10715005	Vasoconstriction	Collected throughout	None	None
DSXS-0904	Phototoxicity			
Multiple Applications				
DSXS-0905	Photo-allergenicity	Collected throughout	None	None
DSXS-0804	Irritation / sensitization		Seated blood pressure pre-dose and on Days 4, 11, and 22 (product removed) and Day 36 (start of sensitization/ challenge) and final study visit Pulse, temperature and respiratory rate pre-dose, Day 36, and final study visit	
DSXS-0805	HPA axis suppression		Baseline and the final study visit (Day 28)	

Phase 1 Dermal Safety Trials

The applicant conducted 3 provocative dermal safety trials in healthy adult subjects with the to-be-marketed formulation to support the safety of desoximetasone topical spray. These trials evaluated the potential for irritation and sensitization (DSXS-0804), phototoxicity (DSXS-0904) and photoallergenicity (DSXS-0905).

DSXS-0804

Title: A Multiple Site Study to Evaluate the Cumulative Skin Irritation and Sensitization Potential of Desoximetasone 0.25% and 0.05% Topical Sprays Compared to Positive and Negative Controls, a Vehicle Formulation and Clobex® (clobetasol propionate) Spray, 0.05%

Study Plan

This was a multicenter (3 sites), evaluator blinded, within-subject, randomized trial to evaluate the potential of desoximetasone 0.25% and 0.05% spray to induce cutaneous irritation and sensitization in 297 healthy adult volunteers. The comparators included: positive control (0.1% sodium lauryl sulfate solution), vehicle spray, negative control (0.9% sodium chloride solution) and Clobex® (clobetasol propionate) Spray, 0.05% (Class 1 corticosteroid.)

Investigators applied 0.5 mL of each of the six test products on the right upper mid back of each subject during the irritation/induction phase of the trial and the left upper mid

back during the sensitization/challenge phase of the trial. The induction phase involved a 21- day cumulative exposure to the six test products under occlusive patches. On Day 22 (30 minutes after removing the patches), evaluators recorded the signs and symptoms of irritation using the scale described in Table 36.

Following a 14- day rest period, investigators applied the 6 test products under occlusive patches to naïve sites on the left back for 48 hours. After the test products were removed, the sites were evaluated for sensitization effects with the scale presented in Table 36.

Table 36: Scale for Rating Dermal Responses

DERMAL RESPONSE[1]		OTHER EFFECTS[2]	
Score	**Skin Appearance**	**Score**	**Observation**
0	No evidence of irritation	0	No other observations or slightly glazed appearance
1	Minimal erythema, barely perceptible		
2	Definite erythema, readily visible; or minimal edema or minimal papular response	1	Marked glazed appearance
3	Strong erythema; or erythema and papules	2	Glazing with peeling and cracking observed
4	Definite edema	3	Glazing with fissures
5	Erythema with edema and papules		Film dried serous exudates covering all or part of the application site
6	Vesicular eruption		Small petechial erosions and/or scabs
7	Strong reaction spreading beyond application site		

[1] This scale is used for the primary analysis of irritation. If the evaluator observes other signs of possible local skin irritation, he or she may use the Other Effects rating scale to describe the type and severity of other localized reactions.
[2] Observation of any of these were to result in a numeric addition to the total irritation or sensitization scores.

Results

A total of 297 healthy adult subjects (127 males, 170 females) were enrolled and 269 completed the 21 day induction phase of the trial. A majority of the study population were African American (174 subjects, or 58.6%) while 71 subjects were Caucasian (23.9%). The mean age was 35 years with a range of 18 to 67 years. Among the 28 subjects who discontinued the trial during the induction phase, none discontinued due to excessive irritation. Three subjects were discontinued from the trial due to adverse events 1) nausea vomiting and loose stools; 2) bilateral hand rash and generalized itching and 3) increased blood pressure.

There were no dermal response scores that were greater than “3.” However, 4 subjects across the three treatment groups had at least one reported score of “3” on Day 22 (3 subjects at the desoximetasone topical spray, 0.25% site, 1 subject at the desoximetasone topical spray, 0.05% site, and 1 subject at the vehicle site).

The mean cumulative irritation score for desoximetasone topical spray, 0.25% was 0.51.

Reference ID: 3252617

Table 37: Mean Total Irritation Scores on Day 22 (N=269 Completers)

		Desoximetasone		Vehicle
		0.25%	0.05%	
	n	268	269	269
Day 22	Mean ± SD	0.51 ± 0.84	0.40 ± 0.77	0.06 ± 0.32
	Median (Range)	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)

Source: DSXS-0804 Clinical Study Report, Table 1

A total of 254 subjects enrolled in the sensitization phase of the trial and 251 subjects were exposed to the test product for at least 44 hours. Seventeen subjects were discontinued from this phase of the trial and two had adverse events (acute pharyngitis, pregnancy).

The threshold for sensitization was defined as a total (combined) score of ≥ 2 at 48 or 72 hours after patch removal. No subject met these criteria.

Therefore, desoximetasone topical spray has no irritation and sensitization potential under these study conditions.

Trial DSXS-0904 and Trial DSXS-0905 were designed to assess the phototoxicity and photoallergenicity of desoximetasone topical spray, 0.25% and 0.05% compared with vehicle spray. An untreated non-occluded site served as a control. Enrolled subjects were healthy adult males and non-pregnant females with Fitzpatrick Skin Type I-III and no dermatologic or systemic disorder that would interfere with the trial assessments.

Trial DSXS-0904
Title: A 4-Day, Randomized Study to Evaluate the Irritation Potential of Desoximetasone 0.25% and 0.05% Topical Sprays When Application to the Skin is Followed by Light Exposure in Healthy Volunteers, Using a **Phototoxicity** Patch Test Design.

Study Plan: This was a single-center, randomized, controlled, within-subject trial to assess the phototoxic potential of desoximetasone 0.25% and 0.05% sprays in 39 healthy subjects. After determining the Minimal Erythemal Dose (MED) for each subject, investigators identified 2 sets of three sites on the infrascapular back of each subject and applied 0.2 mL of desoximetasone topical spray, 0.25%, desoximetasone topical spray, 0.05% and vehicle spray to one site in each set. Semi-occlusive patches were applied to each 4 cm^2 site. Approximately 24 hours after application, investigators removed the patches and irradiated one set of sites as well as an untreated control site with 6 J/cm^2 of UVA (320-400 nm) followed by 0.5 times the MED of UVA/UVB (290-320 nm). The investigator evaluated all sites with a visual scale upon patch removal and approximately 24, 48, and 72 hours after irradiation. On Days 2 through 4, the investigators assessed all treatment areas for local tolerability using the following scale.

Table 38: Response Grading Scale

Grading Responses			Response Notations	
Response	Symbol	Score	Response	Notation
Erythema			Hyperpigmentation	Hr
No reaction	-	0	Hypopigmentation	Ho
Mild but definite erythema	+	1.0	Vesiculation	V
Moderate erythema	++	2.0	Papular response	P
Marked/severe erythema	+++	3.0	Papulovesicular response	pv
Edema			Damage to epidermis: oozing, crusting and/or superficial erosions	D
Mild, but definite edema	**	1.0	Itching	I
Definite edema with erosion/vesiculation	***	1.5	Spreading of reaction beyond patch study site	S
			Follicular irritation with or without pustule formation	f
			Subject absent	X
			Patch dislodged	PD
			Not patched	NP

Source: Modified from NDA 204141; Clinical Study Report DSXS-0904; Table 3.3 and Table 3.4

Results:
Mild erythema was evident at the irradiated treatment sites of desoximetasone topical spray 0.05% and 0.25% (mean score for each 0.88), and vehicle spray (mean score 0.162) at 24 and 48 hours after irradiation. In addition, mild erythema was evident at the untreated irradiated site (mean 0.338). Mean irritation scores were significantly greater in the irradiated sites compared with the non-irradiated sites and in the treated irradiated sites compared with the untreated irradiated site. Thus, subjects experienced no phototoxicity under these trial conditions.

Table 39: Summary of Results of Trial DSXS-0904

Study Medication	Irradiated Average of Day 3 and 4 Mean (± SD)	Non-Irradiated Average of Day 3 and 4 Mean (± SD)	*P* Value								
			A Irrd vs B Irrd	A Irrd vs A Non-Irrd	B Irrd vs. B Non-Irrd	A Irrd vs C Irrd	B Irrd vs C Irrd	C Irrd vs. C Non-Irrd	A Irrd vs D Irrd	B Irrd vs D Irrd	C Irrd vs. D Irrd
Desoximetasone 0.25% (A)	0.088 (0.193)	0.000 (0.000)	1.000	**0.040**		0.086			**<.001**		
Desoximetasone 0.05% (B)	0.088 (0.193)	0.000 (0.000)			**0.040**		0.086			**<.001**	
Vehicle (C)	0.162 (0.294)	0.000 (0.000)						**<.001**			**<.001**
Untreated (D)	0.338 (0.294)	—									

Note: Irrd = irradiated; Non-IRRD = nonirradiated.
Source: Post-text Table 14.2

Trial DSXS-0905
Title**:** A 6-Week, Randomized Study to Evaluate the Potential of Desoximetasone 0.25% and 0.05% Topical Sprays and Vehicle to Induce a **Photoallergic Skin Reaction** in Healthy Volunteers, Using a Controlled Photopatch Test Design

Study Plan: This was a single-center, randomized, controlled, within-subject trial to assess the photoallergic potential of desoximetasone 0.25% and 0.05% sprays compared to the vehicle spray in 58 healthy subjects. The procedures during the induction Phase were the same as Trial DSXS-0904. At the end of the induction period, subjects entered a rest period of 10-17 days. After completion of the rest period, investigators applied each of the 3 study products to 2 naïve sites (6 total sites) and covered them with semi-occlusive patches. After 24 hours, investigators removed the patches and irradiated one of each pair of sites and one untreated site. Investigators recorded the dermal reactions at 24, 48 and 72 hours after irradiation. Refer to the Table 38 for the Response Grading Scale.

Results
A total of 53 healthy adult male and female subjects completed the trial. The majority of subjects were female (78%), White (98%) and non-Hispanic/Latino (93%) with Fitzpatrick Skin Type III (69%). The mean age was 48 years with a range of 20 to 70 years.

Investigators observed no more than mild erythema following final irradiation of the application sites treated with desoximetasone topical spray 0.25%, desoximetasone topical spray 0.05%, and vehicle spray. The non-irradiated sites treated with desoximetasone topical spray showed no reaction.

Thus, photoallergy was not elicited with desoximetasone topical spray under these study conditions.

Among the 5 of subjects who discontinued the trial, 2 subjects experienced an adverse event (herpes virus infection and back injury), 2 subjects withdrew consent and 1 subject withdrew for other reasons.

There were a total of 10 AEs reported by 6 subjects. None of the AEs reported were serious or severe. Investigators assessed all the AEs as unrelated or unlikely to be related to the study products. The only adverse event reported by more than other subject was nasopharyngitis. Other AEs included: viral eye infection, herpes zoster, oral herpes, upper abdominal pain, pyrexia, back injury, back pain and nasal congestion.

Phase 1: HPA Axis Suppression and Vasoconstriction Trials
Trial DSXS-0805

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

Study Plan:
This was an open label, multicenter (3) trial to assess systemic exposure and the effect of desoximetasone 0.25% topical spray on the hypothalamic-pituitary axis in 24 subjects 18 years of age or older with a confirmed diagnosis of moderate to severe plaque psoriasis. Investigators enrolled subjects into one of 2 cohorts: 12 with involvement of 10-15% of their body surface area and 12 with involvement of > 15% of their body surface area. Screening assessments included Baseline cortisol response. Subjects applied the study product twice daily for 28 days

Refer to Section 4.4, 7.2.5 and 7.2.6 for further information regarding the evaluation of HPA axis suppression and plasma desoximetasone concentration.

Results:
The FDA defines HPA suppression as a response to cosyntropin stimulation which is less than 18 µg/dL 30 minutes after stimulation. After excluding 3 subjects whose data could not be validated, 3 out of 21 subjects (14%) had a serum cortisol concentration at Day 28 that met at the criteria for adrenal suppression. Refer to Section 4.4, 7.2.5 and 7.2.6 for a discussion of the results of Trial DSXS-0805. The data is tabulated below.

Table 40: Desoximetasone Plasma Concentrations Following Application Twice Per Day for 28 Days

Subject Number	Age / Sex	Serum Cortisol Concentrations (µg/dL)								
		Pre-Treatment			Day 28			Follow-Up		
		Basal	Post	Change	Basal	Post	Change	Basal	Post	Change
10-15% BSA Affected (mean age 52.1 ± 15.0 years)										
02-212	61 / F	10.6	18.5	7.9	5.3	17.9*	12.6	Lost to follow-up		
02-226	42 / M	9.5	23.9	14.4	4.6*	22.0	17.4	14.8	25.6	10.80
> 15% BSA Affected (mean age 46.8 ± 19.5 years)										
02-203	57 / F	12.1	32.2	20.1	4.2*	17.9*	13.7	9.8	23.5	13.70
02-211	70 / M	11.2	20.3	9.1	6.4	17.9*	11.5	10.3	18.7	8.40
03-302	39 / F	13.8	26.6	12.8	1.2*	23.2	22.0	Lost to follow-up		

Source: NDA 204141, Clinical Study Report for Trial DSXS-0805
:

There was no statistically significant difference in the plasma desoximetasone concentrations in the subjects with HPA axis suppression as compared to subjects without HPA axis suppression. The Clinical Pharmacology reviewer states "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 41:Desoximetasone Plasma Concentrations Among Subjects Who Experience HPA Axis Suppression Compared with Those Who Did Not Experience HPA Axis Suppression.

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: NDA 204141, clinical Study Report for Trial DSXS-0805, Table 6

Trial 10715005

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

Study Products:

- Desoximetasone 0.25% Topical Spray
- Placebo Spray
- Clobex® (clobetasol propionate) 0.05% Spray
- Topicort® (desoximetasone) 0.25% Cream
- Flucinonide 0.05% Ointment
- Elocon® (mometasone furoate) 0.1% Ointment

- Topicort® LP (desoximetasone) 0.05% Cream
- Cultivate® (fluticasone propionate) 0.05% Cream
- Hytone® (hydrocortisone) 2.5% Cream

Study Plan:
The trial was a randomized, evaluator blinded, within subject, single-center assessment of the vasoconstrictive properties of desoximetasone topical spray 0.25%, compared to seven other corticosteroid formulations and placebo spray in 32 healthy non-smoking adult subjects.. Enrolled subjects had a demonstrated blanching response to fluticasone propionate cream 0.05%, body mass index (BMI) 30 kg/m² or less and no medical or dermatologic condition which would interfere with the assessments. The majority of subjects were African American (62.5%), female (90.6%) with mean age of 25 years (range 18-47 years). Investigators identified 11 sites on the forearms of each subject which were 2 cm apart. Nine of the 11 sites on each forearm were treated with a study product and 2 sites on each forearm were left untreated. The degree of vasoconstriction was measured using a ChromaMeter and visual scoring at Baseline (2 hours before application) and 18 hours after application. Investigators used the following visual scale to grade vasoconstriction:

0 = No pallor; no change from surrounding area.
1 = Mild pallor; slight or indistinct outline of application site.
2 = Moderate pallor; discernible outine of application site.
3 = Intense pallor; clean, distinct outline of application site.

Results
The degree of vasoconstriction induced by desoximetasone topical spray 0.25% was equivalent to Elocon (mometasone furoate) 0.1% Ointment when assessed by visual scoring and between Topicort (desoximetasone) 0.25% Cream and Clobex (clobetasol propionate) 0.05% Spray when assessed by ChromaMeter scoring. Thus, desoximetasone topical spray 0.25% may be categorized as a Class 1 or Class 2 corticosteroid. Refer to Table 42 for a summary of these findings and the Clinical Pharmacology Review dated 1/18/2013.

Table 42: Results of the Vasoconstriction Trial as Assessed by Mean Visual Score and ChromaMeter Score

Formulation	Mean visual Score	ChromaMeter Score
Desoximetasone 0.25% Topical Spray	1.1563	-1.1986
Clobex (clobetasol propionate) 0.05% Spray	1.1094	-1.1258
Topicort (desoximetasone) 0.25% Cream	1.2969	-1.3625
Flucinonide 0.05% Ointment	1.3125	-1.0773
Elocon (mometasone furoate) 0.1% Ointment	1.1563	-0.9959
Topicort LP (desoximetasone) 0.05% Cream	0.9375	-0.9463
Cultivate (fluticasone propionate) 0.05% Cream	0.6406	-.0.4933

Hytone® (hydrocortisone) 2.5% Cream	0.2344	-0.0463
Placebo	0.0156	-0.0344
untreated	0.000	0.0002

Source: NDA 204141, Table 1, Clinical Study Report 10715005

Thus, labeling of desoximetasone topical spray 0.25% as a "super-high potency corticosteroid" is not supported.

7.4.6 Immunogenicity

The potential for immunogenicity was not anticipated or assessed since the drug product is not a therapeutic protein.

7.5 Other Safety Explorations

The applicant submitted the results of a search of the worldwide published literature conducted on May 4, 2011 and updated on December 5, 2011 and September 6, 2012.. The applicant conducted a search of the published literature from multiple databases (MEDLINE®, Biosis Previews®, and EMBASE®) to collect citations regarding clinical safety information for desoximetasone/ Topicort® from 2004 (Taro purchased theTopicort® brand in 2003) to December 5, 2011. The 3 searches identified 108 citations which are summarized in the following table.

Table 43: Results of the worldwide published literature search

Types of Content from 108 Total Citations	No. of Citations
General reviews of topical corticosteroids and treatments for psoriasis, atopic dermatitis, and other skin conditions	42 (39%)
Other articles unrelated to the search topic	35 (32%)
Reports of safety or efficacy of other treatments for skin conditions	12 (11%)
Reports of dermatitis or other skin conditions in which topical corticosteroids are used for treatment	11 (10%)
Case reports or review of possible safety information related to desoximetasone • 7 publications ordered for full review, of which 1 is included in the Summary of Safety and 6 were not specific to desoximetasone • 1 publication was a labeled event	8 (7%)

Source: NDA 204141 SD-11, pg.9

The majority of the 108 unique citations was general reviews, reports involving the treatment of various skin conditions with topical corticosteroids, unrelated to use of topical corticosteroids or unrelated to the safety of desoximetasone. The applicant included a single case report of cross sensitivity of desoximetasone with mometasone in the safety database. In this citation, Donovan and Dekoven (2006) describe a 60 year-old man with an atopic diathesis who was treated with betamethasone dipropionate

(formulation not indicated) for a localized patch of dermatitis on his lower leg. His physician prescribed Fluocinonide (formulation not indicated) when the patch of dermatitis failed to resolve with betamethasone. Subsequently, the subject observed redness, itching, and blister formation at the application site. Patch testing confirmed contact dermatitis to desoximatasone with cross reactions to numerous Group B and Group D corticosteroids (defined according to substitutions at C16/C17 or C21) including mometasone.

7.5.1 Dose Dependency for Adverse Events

Although the applicant did not include trials in the development program which were designed to assess dose dependency of adverse events, there is some data from trial DSXS-906 and DSXS-805. During trial DSXS-906, subjects applied either desoximetasone topical spray 0.05% or desoximetasone topical spray 0.25% once or twice daily. There was no significant difference in the adverse event profile between dosing groups.

Subjects enrolled in Trial DSXS-805 had plaque psoriasis affecting 10-15% BSA or plaque psoriasis affecting >15% BSA. The pattern of adverse events was not significantly different in the 2 treatment groups based on the amount of exposure to desoximetasone topical spray.

Table 44: Summary of Adverse Events by Percent BSA Affected by Psoriasis

Following the Application of desoximetasone topical spray for 28 Days

MedDRA System Organ Class MedDRA Preferred Term	BSA 10-15% n=12	BSA >15% n=12	Total N=24
No. reporting AEs	3 (25.0%)	6 (50.0%)	9 (37.5%)
Endocrine Disorders			
Adrenal Suppression*	2 (16.7%)	3 (25.0%)	5 (20.8%)
Gastrointestinal Disorders			
Vomiting	0	1 (8.3%)	1 (4.2%)
General Disorders and Administration Site Conditions			
Application Site Pruritus	0	1 (8.3%)	1 (4.2%)
Musculoskeletal and Connective Tissue Disorders			
Sciatica	0	1 (8.3%)	1 (4.2%)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)			
Cyst	0	1 (8.3%)	1 (4.2%)
Nervous System Disorders			
Abnormal Dreams	1 (8.3%)	0	1 (4.2%)
Carpal Tunnel Syndrome	1 (8.3%)	0	1 (4.2%)
Headache	2 (16.7%)	0	2 (8.3%)
Vascular Disorders			
Hypertension	1 (8.3%)	0	1 (4.2%)

Source: Table 29, Integrated Summary of Safety

7.5.2 Time Dependency for Adverse Events

The applicant did not include trials in the development program which were designed to compare time to onset of adverse events.

7.5.3 Drug-Demographic Interactions

Analysis of adverse events by age (≤65 versus >65) and race (White versus Non-white) was cofounded by the limited numbers of subjects > 65 years old and Non-white subjects. There were 59 subjects who were ≥ 65 years old and 17 subjects who were ≥75 years old and 15 subjects who were self-identified as Non-White. The following trends were suggested by the data:

- Subjects who were ≥ 65 years reported a greater number of treatment emergent adverse events and application site reactions,
- Non-white subjects reported a greater number of application site reactions
- Hispanic/Latino subjects reported lesser number of treatment emergent adverse events and application site reactions

The significance of these findings is not clear based on the limitations of the database. Refer to Table 45 and Table 46.

Table 45: Treatment Emergent Adverse Events by Age and Sex (Safety Population)

Study Product	Age: 18-65 years	Age: >65 years	Sex: Female	Sex: Male
Topicort Spray				
No. of Subjects	126	23	52	97
No. AEs (%)*	22 (17.5)	7 (30.4)	9 (17.3)	20 (20.6)
No.Application** site AEs (%)	8 (6.3)	3 (13.0)	5 (9.6)	6 (6.2)
Vehicle Spray				
No. of Subjects	99	36	49	86
No. AEs (%)	27 (27.3%)	11 (30.6)	20 (40.8)	18 (20.9)
No.Application site AEs (%)	12 (12.1%)	6 (16.7)	10 (20.4)	8 (9.3)

*Number of subjects with a treatment emergent adverse events
** Number of subjects with a treatment emergent adverse events classified under the preferred term of application site dryness, application site irritation, application site pruritus, application site pain, application site erythema, application site rash
Source: NDA 204141 SD 11, Section 14 Extended Tables pg 215-233

Table 46: Treatment Emergent Adverse Events by Race and Ethnicity (Safety Population)

Study Product	Race: White	Race: Non-White	Ethnicity: Hispanic/Latino	Ethnicity: Not Hispanic/Latino
Topicort Spray				
No. of Subjects	143	6	29	120
No. AEs (%)*	28 (19.6)	1 (16.7)	2 (6.9)	27 (22.5)
No.Application site AEs (%)	10 (7.0)	1 (16.7)	1 (3.4)	10 (8.3)
Vehicle Spray				
No. of Subjects	126	9	22	113
No. AEs (%)	36 (28.6)	2 (22.2)	4 (18.2)	34 (30.1)
No.Application site AEs (%)	18 (14.3)	0	1 (4.5)	17 (15.0)

*Number of subjects with a treatment emergent adverse events
** Number of subjects with a treatment emergent adverse events classified under the preferred term of application site dryness, application site irritation, application site pruritus, application site pain, application site erythema, application site rash
Source: NDA 204141 SD 11, Section 14 Extended Tables pg 215-233

7.5.4 Drug-Disease Interactions

The applicant conducted no formal analyses on the data regarding desoximetasone topical spray for potential drug-disease interactions and provides no information regarding the safety profile in subjects with hepatic or renal dysfunction or other concurrent diseases.

7.5.5 Drug-Drug Interactions

Drug interactions with desoximetasone topical spray were not evaluated given the low systemic absorption of topically applied desoximetasone. Drug interactions are not included in the current approved labeling for other topical desoximetasone formulations.

7.6 Additional Safety Evaluations

Refer to Section 7.5 of this review.

7.6.1 Human Carcinogenicity

There were no formal analyses of data to explore human carcinogenicity.

Refer to Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility of labeling.

7.6.2 Human Reproduction and Pregnancy Data

Desoximetasone products as well as other members of this pharmacologic class are identified as Pregnancy Category C in labeling. Section 8.1 of the proposed labeling contains the following statement:

> Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. (b) (4) [redacted] (b) (4) There are no adequate and well-controlled studies in pregnant women [redacted] (b) (4) Topicort® [redacted] (b) (4) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (b) (4) [redacted]

The Agency recommended the following labeling for Sections 8.1 and 8.3.

> **8.1 Pregnancy**
> Teratogenic Effects: Pregnancy Category C
>
> There are no adequate and well-controlled studies in pregnant women. Topicort Topical Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
>
> Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels.
>
> Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration at doses 3 to 30 times the human dose of Topicort Topical Spray based on a body surface area comparison.
>
> **8.3 Nursing Mothers**
> Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when Topicort Topical Spray is administered to a nursing woman.
>
> If used during lactation, Topicort Topical Spray should not be applied on the chest to avoid accidental ingestion by the infant.

7.6.3 Pediatrics and Assessment of Effects on Growth

In the NDA submission, the applicant included a request for a waiver of the requirement to complete a pediatric assessment for children with psoriasis who are [redacted] (b) (4). The justification for waiving the pediatric assessment requirements is:

- [redacted] (b) (4)
- [redacted] (b) (4) {Section 8.4 of the proposed labeling describes the safety concern. (e.g. risk of HPA axis suppression, Cushing's syndrome, and intracranial hypertension)}

In addition, the applicant states that desoximetasone topical spray, 0.25%, is [redacted] (b) (4)

The Pediatric and Maternal Health Staff Reviewers Elizabeth Durmowicz, MD and Hari Sachs, MD, recommended the following approach to the assessment of pediatric patients as required by PREA for Topicort topical spray (Consult dated 12/3/2012):

> "A partial waiver in pediatric patients less than 2 years of age is reasonable based on the epidemiology of pediatric psoriasis. However, given the lack of pediatric HPA axis suppression data with desoximetasone, and the risk/benefit ratio posed by alternative therapies, PMHS recommends the sponsor be asked to submit a pediatric plan addressing patients 2 years and older, which outlines studying HPA axis suppression; first in adolescents and then in younger children before proceeding to any confirmatory efficacy studies. In order to support their waiver request, the sponsor should also submit topical steroid use data for class 1 and 2 products to augment the epidemiological data that has been provided."

Ali Mohamadi, MD, Division of Metabolism and Endocrinology Products (DMEP) provided the following recommendations regarding the conduct of the HPA axis evaluation in pediatric subjects (Consult dated 12/5/2012):

- We would recommend that testing be performed as per the "standard" protocol, namely a cosyntropin dose of 250 µg, with serum cortisol levels measured at T=0, 30, and 60 minutes, with a cutoff value of >18 µg/dL at any point of time being considered normal.

- Given the short-term nature of the study, the most useful safety assessments would include cosyntropin (ACTH) stimulation testing at baseline and Day 28, as well as weekly physical examinations to rule out the signs and symptoms

(including hypotension and/or tachycardia, weakness/lethargy, fatigue, vomiting, and dehydration.)

DMEP agrees with PMHS's recommendation for enrollment of pediatric patients: evaluation of desoximetasone in patients aged 12-16 years should be performed first before moving to younger pediatric patients. If studies show significant HPA axis suppression in adolescents, a partial waiver for younger patients would be a reasonable consideration, with labeling to be updated to reflect the safety concern.

After Agency recommendations were communicated to the applicant (12/3/2012), Taro submitted a Pediatric Development Plan (SD 20, dated 12/19/2012.) The proposed HPA axis suppression trial included (b) (4) evaluable subjects ages 2 years to 16 years 11 months with (b) (4)

The Pediatric Review Committee (PeRC) concurred with the Division's proposal to require the conduct of a safety trial in sequential cohorts (based on age) which included 100 evaluable subjects with plaque psoriasis ages 2 years to 16 years 11 months (1/9/2013). The safety evaluation would include: an evaluation of HPA axis suppression and pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment, vital signs, physical examinations, local safety, and adverse events. These comments regarding the assessment of pediatric patients required under PREA were communicated to the applicant on 1/16/2013.

On 1/17/2013 the applicant submitted a revised Pediatric Waiver to complete a pediatric assessment for children with psoriasis who are <2 years of age based on the increased risk of local and systemic side effects, including growth retardation, as a result of higher skin surface to body mass ratio and a Request for Deferral of Pediatric Study. The applicant proposed to meet the requirement to evaluate desoximetasone 0.25% topical spray for the treatment of plaque psoriasis in pediatric subjects by conducting " an open-label study to assess the potential for adrenal suppression following multiple dosing with desoximetasone 0.25% Topical Spray in pediatric patients with psoriasis."

Postmarketing requirement under PREA:

Conduct a trial in 100 evaluable pediatric patients with psoriasis (b) (4) ages 2 to 16 years and 11 months. Evaluate the safety and effect of desoximetasone topical spray, 0.25% on the hypothalamic-pituitary axis and pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment. Conduct the trial 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

Final Protocol Submission: 4/30/2014

Trial Completion: 4/30/2016
Final Report Submission: 4/30/2017

Safety assessments should include: vital signs, physical examinations, local safety, and adverse events.

We are deferring submission of the pediatric trial described above for ages 2 to 16 years and 11 months for this application because this product is ready for approval for use in adults and the pediatric trial has not been completed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant states that there is no information regarding the abuse potential of desoximetasone and no reports of overdose during the clinical trials conducted in support of the NDA.

The trials in the development program were not designed to assess rebound after withdrawal of the drug product.

7.7 Additional Submissions / Safety Issues

The applicant assigned the following functions to formulation excipients:

- Glyceryl oleate (b) (4)
- Isopropyl myristate (b) (4)
- L-Menthol (b) (4)
- Mineral oil (b) (4)

These are clinical claims that require supporting data as they cannot be substantiated using the physicochemical properties of the excipients alone. Since this supporting data was not provided in the NDA, the Division requested clarification of the physiochemical function of the excipients or submission of additional data (letter dated August 15, 2012.) In a letter dated September 28, 2012, the applicant stated that these functions were recognized in the Handbook of Pharmaceutical Excipients Fifth Edition but revised the functions of the formulation excipients as follows:

- Glyceryl oleate - (b) (4)
- Isopropyl myristate- (b) (4)
- L-Menthol (b) (4)
- Mineral oil- (b) (4)

These revised physiochemical functions are acceptable. Refer to the CMC Review.

8 Postmarket Experience

There were two sources of postmarketing adverse event data submitted with this NDA application: adverse event data from FDA databases and adverse event data from applicant databases.

The applicant submitted a review of the postmarketing adverse events reported to the Agency for all desoximetasone products. There were a total of 252 adverse event reports in the Agency databases. Table 47 presents a summary of the most common adverse events reported in association with desoximetasone in the FDA postmarketing databases (ADR and AERS) from 1977 through 9/30/2011. The most common adverse events associated with desoximetasone use prior to 1997 were rash, pain, and application site reaction. In contrast, after the utilization of the AERS database in 1997, the most common adverse events were alopecia, condition aggravated and skin discoloration. The adverse event of "alopecia" is not included in the proposed labeling.

Table 47: Most Common AEs Reported in Association with Desoximetasone in FDA Postmarketing Databases (ADR ≥ 5 Reports and AERS ≥ 2 Reports**)**

FDA SRS Database ≥ 5 reports 1977 – 31 Oct 1997 COSTART Term	No. Reports	FDA AERS Database ≥ 2 reports (Nov 1997 – 30 Sep 2011) MedDRA Preferred Term	No. Reports
Rash	31	Alopecia	4
Pain	24	Condition Aggravated	3
Application Site Reaction	22	Skin Discolouration	3
Lack of Drug Effect	22	Application Site Burn	2
Allergic Reaction	18	Application Site Pigmentation Changes	2
Contact Dermatitis	18	Burning Sensation NOS	2
Pruritus	18	Cushing's Syndrome	2
Skin Striae	11	Dermatitis NOS	2
Aggravation Reaction	10	Drug Maladministration	2
Acne	8	Erythema	2
Skin Discoloration	7	Herpes Zoster	2
Skin Disorder	7	Neuralgia	2
Urticaria	7	Oedema Peripheral	2
Skin Atrophy	6	Pain in Extremity	2
Vesiculobullous Rash	6	Pruritus	2
Dizziness	5	Psoriasis Aggravated	2
Face Edema	5		
Paresthesia	5		
Reaction Unevaluable	5		

Source: NDA 204141 Section 2.7 Clinical Summary, pg. 37

The applicant database includes adverse event (AE) reports received for all Topicort formulations. The initial submission included adverse event (AE) reports received after

Reference ID: 3252617

the review period for the last annual report for all Topicort® products through 12/31/2011. The last annual report date for each NDA/ANDA is listed in the following table:

Table 48: Annual Report Dates for Desoximetasone NDAs/ANDAs

Application Number	Product	Most Recent Annual Report Cut-off Date
NDA 18-594	Desoximetasone Ointment USP 0.05%	16 January 2011
NDA 18-763[1] ANDA 74-286	Desoximetasone Ointment USP 0.25%	6 June 2011
NDA 18-586[1] ANDA 74-904	Desoximetasone Gel USP 0.05%	13 July 2011
NDA 18-309[1] ANDA 73-210	Desoximetasone) Cream USP 0.05%	29 November 2011
NDA 17-856[1] ANDA 73-193	Desoximetasone Cream USP 0.25%	29 November 2011

In the initial submission the applicant described one case submitted to ANDA 74-904 regarding desoximetasone gel USP 0.05% which involved the exacerbation of an unidentified hand dermatitis following application of the product “for several days.” In an update submitted on 10/17/2012, the applicant provided 13 additional reports which were submitted to Taro for all desoximetasone formulations through 9/1/2012. Two of these cases were submitted as expedited 15 day reports (2012P1025775; 2012P1022208)

Table 49: AE Reports Regarding Desoximetasone Submitted Through 9/1/2012

NDA Number	Product	N Cases[2]	Events Reported (Case No.)
NDA 18-594	Desoximetasone Ointment USP 0.05%	2	Vitiligo (2012P1023473)
			Drug ineffective (2012P1048060)
NDA 18-763[1] ANDA 74-286	Desoximetasone Ointment USP 0.25%	1	Drug ineffective (2012P1003411)
NDA 18-586[1] ANDA 74-904	Desoximetasone Gel USP 0.05%	1	Burning sensation, Erythema (2012P1018473)
NDA 18-309[1] ANDA 73-210	Desoximetasone Cream USP 0.05%	4	Drug ineffective, Depression, Condition aggravated, Skin haemorrhage, Malignant melanoma, Skin exfoliation, Blister, Skin discolouration, Erythema, Squamous cell carcinoma[3] (2012P1025775)
			Condition aggravated (2012P1045045)
			Drug ineffective (2012P1049363)
			Application site pain (2012P1053243)
NDA 17-856[1] ANDA 73-193	Desoximetasone Cream USP 0.25%	5	Blister, Pruritus, Haemorrhage, Rash macular (2012P1004122)
			Application site pain, Skin irritation, Pruritus, Skin warm, Erythema, Skin exfoliation, Lupus-like syndrome (2012P1009933)
			Application site erythema, Application site swelling, Application site pruritus (2012P1010821)
			Tinea pedis, Pruritus, Aphthous stomatitis, Incorrect route of drug administration, Dandruff, Off- label use, Skin exfoliation, Urinary control neurostimulator implantation[3] (2012P1022208)
			Urticaria, Pruritus (2012P1044243)

1 Product not currently marketed as Topicort®
2 Received by Taro since the original Summary of Safety
3 Case was reported as an expedited 15-day report
Source: NDA 204141 SD 11; Summary of Clinical Safety pg. 38

Adverse events reported in Table 49 which are not included in the proposed labeling include: hemorrhage, depression, malignant melanoma, squamous cell carcinoma, lupus- like syndrome and aphthous stomatitis. Hemorrhage is the only adverse event reported in more than one patient and may be associated with blistering.

In addition per Advice Letter dated 10/2/2012, the applicant provided a list of 14 cases involving 32 adverse events compiled during the annual reporting periods prior to the submission of the NDA.

Reference ID: 3252617

Table 50: AEs Reported During the Annual Reporting Periods Prior to the Submission of the NDA

NDA Number	Product	N Cases	Events Reported (Case No.)
NDA 18-594	Desoximetasone Ointment USP 0.05%	0	N/A
NDA 18-763[1] ANDA 74-286	Desoximetasone Ointment USP 0.25%	3	Drug ineffective (1-23134272)
			Blepharitis (2010P1002870)
			Burning sensation, Rash, Pruritus, Blister (2011P1005903)
NDA 18-586[1] ANDA 74-904	Desoximetasone Gel USP 0.05%	3	Diarrhea, Abdominal pain, Pruritus (2010P1001843)
			Headache, Skin discoloration, Drug effect decreased[2] (2010P1002496)
			Accidental exposure, Foreign body sensation in eyes, Corneal erosion, Eye discharge[2] (2011P1006631)
NDA 18-309[1] ANDA 73-210	Desoximetasone Cream USP 0.05%	2	Dizziness, Dyspnea, Hypersensitivity, Balance disorder (2011P1006325)
			Flushing (2011P1010154)
NDA 17-856[1] ANDA 73-193	Desoximetasone Cream USP 0.25%	6	Skin exfoliation, Drug ineffective (2011P1004857)
			Rash (2011P1007071)
			Erythema, Burning sensation (2011P1007195)
			Drug effect decreased, Off label use 2011P1007294)
			Rash, Blister, Dermatitis (2011P1008699)
			Application site discoloration (2011P1008788)

Source: NDA 204141 SD-11, Clinical Summary, Pg. 38

All of the adverse events reported in Table 50 are included in the (b) (4)

Based on the duration of the postmarketing period for the moiety (>35 years), it is likely that significant new adverse reactions associated with desoximetasone would be well supported. After review of the postmarketing adverse event reports from the FDA databases (SRS and AERS) since 1977, postmarketing adverse event reports submitted to the applicant and the search of the world wide literature, no safety new safety signals are identified.

9 Appendices

9.1 Literature Review/References

Agner T, Serup J. Sodium lauryl sulphate for irritant patch testing - a dose-response study using bioengineering methods for determination of skin irritation. J Invest Derm 1990; 95:543-547.

Berardesca E, Maibach H. Racial differences in skin pathology. J Am Acad Dermatol 1996; 34(4): 667-672.

Donovan JCH, DeKoven JG. Cross-reactions to Desoximetasone and mometasone furoate in a subject with multiple topical corticosteroid allergies. Dermatitis 2006; 17(3):147-151.

Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis 2005;64 Suppl 2:ii65-8.

Garden JM, Freinkel RK. Systemic absorption of topical steroids. Metabolic effects as an index of mild hypercortisolism. Arch Dermatol. 1986 Sep;122(9):1007-10.

Katz HI, Prawer SE, Medansky RS, Krueger GG, Mooney JJ, Jones ML, *et al*. Intermittent corticosteroid maintenance treatment of psoriasis: a double-blind multicenter trial of augmented betamethasone dipropionate ointment in a pulse dose treatment regimen. Dermatologica 1991;183:269-74.

Menter A, Korman NJ, Elmets CA, *et al*. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol 2009;60:643-9.

Miller JJ, Roling D, Margolis D, Guzzo C. Failure to demonstrate therapeutic tachyphylaxis to topically applied steroids in subjects with psoriasis. J Am Acad Dermatol 1999;41: 546-9.

Nestle FO, Kaplan DH, Barker J. Psoriasis. N Eng J Med 2009;361:496-509.

Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): Why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. J Am Acad Dermatol 2012:66:369- 75.

Tollefson MM, Crowson CS, McEvoy MT, *et al*. Incidence of psoriasis in children: A population based study. J Am Acad Dermatol 2010;62:979-87.

Wood JB, Frankland AW, James VHT, Landon J. A rapid test of adrenocortical function. The Lancet 1965;1:243-5.

Wu JJ, Black MH, Smith N, *et al*. Low prevalence of psoriasis among children and adolescents in a large multiethnic cohort in southern California. J Am Acad Dermatol 2011;65:957-64.

9.2 Labeling Recommendations

The applicant submitted labeling in Physician's Labeling Rule (PLR) format which was reviewed by a multidisciplinary team. Labeling negotiations are still in progress as of the date of this clinical review. Refer to reviews by Hamid Shafiei Ph.D. (CMC Review dated 1/23/2012), An-Chi Lu M.S., Pharm.D. (Clinical Pharmacology Review dated 1/18/2013) and Carin Kim, Ph.D. (Statistical Review dated 1/16/2013) for discipline specific recommendations regarding labeling. (Language in blue was inserted and the ~~strikeout~~ language was deleted from the desoximetasone topical spray, 0.25% labeling).

Principal changes to the applicant proposed labeling include the following:

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

(b) (4)

Topicort (b) (4) (b) (4) is a (b) (4) corticosteroid (b) (4) indicated for the (b) (4) treatment of (b) (4) plaque psoriasis (b) (4) in patients 18 years of age or older.

(b) (4)

2 DOSAGE AND ADMINISTRATION

(b) (4)

Apply Topicort® (b) (4) Spray, (b) (4) as a thin film to the affected skin areas twice daily. Rub in gently.
The treated skin area should not be bandaged or otherwise covered or wrapped
Topicort Topical Spray should be discontinued when control is achieved.
Treatment beyond 4 weeks is not recommended.
Do not use if atrophy is present at the treatment site.

Avoid use on the face, axilla or groin.
Topicort Topical Spray is for external use only. It is not for oral, ophthalmic, or intravaginal use.

5 WARNINGS AND PRECAUTIONS

5.1 [redacted] (b) (4) Effect on Endocrine System

Topicort® [redacted] (b) (4) Spray [redacted] (b) (4) is a [redacted] (b) (4) topical corticosteroid that has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Systemic absorption of topical corticosteroids can [redacted] (b) (4) produce reversible [redacted] (b) (4) (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

In a [redacted] (b) (4) including 24 subjects 18 years of age or older with moderate to severe plaque psoriasis, adrenal suppression was identified in 1 out of 12 [redacted] (b) (4) subjects having involvement of 10-15% of body surface area (BSA) and 2 out of [redacted] (b) (4) 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 [redacted] (b) (4) high potency steroids, [redacted] (b) (4) larger treatment surface areas, [redacted] (b) (4) prolonged use [redacted] (b) (4), use of [redacted] (b) (4) occlusive dressings, [redacted] (b) (4) altered skin barrier, [redacted] (b) (4) liver failure and young age.

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.

Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can also result from systemic absorption of topical corticosteroids.

Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.
Pediatric patients may be more susceptible to systemic toxicity from use of topical corticosteroids. [*see Use in Specific Populations (8.4)*]

5.5 Flammable Contents

Topicort Topical Spray is flammable, keep away from heat or flame.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

(b) (4)

In randomized, multicenter, prospective vehicle- controlled clinical trials, subjects with moderate to severe plaque psoriasis of the body applied Topicort Topical Spray or vehicle spray twice daily for 4 weeks. A total of 149 subjects applied Topicort Topical Spray.

Adverse reactions that occurred in ≥1% of subjects treated with Topicort Topical Spray were application site dryness (2.7%), application site irritation (2.7%) and application site pruritus (2.0%).

Another less common adverse reaction (<1% but >0.1%) was folliculitis

(b) (4)

(b) (4)

[redacted]

Table 1. Number (%) of Subjects with Adverse Reactions Occurring in ≥ 1%

	Topicort Topical Spray 0.25% *twice per day* N=149	vehicle spray *b.i.d* N=135
Number of Subjects with Adverse Reactions*	13 (8.7%)	18 (13.3%)
Application site dryness	4 (2.7%)	7 (5.2%)
Application irritation	4 (2.7%)	5 (3.7%)
Application pruritus	3 (2.0%)	5 (3.7%)

(b) (4)

[redacted]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Topicort Topical Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. (b) (4) [redacted]

(b) (4)

Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration at doses 3 to 30 times the human dose of Topicort Topical Spray based on a body surface area comparison.

8.3 Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. (b) (4) Because many drugs are (b) (4) Topicort Topical Spray is administered to a nursing woman.

If used during lactation, Topicort Topical Spray should not be applied on the chest to avoid accidental ingestion by the infant.

8.4 Pediatric Use

(b) (4) Safety and effectiveness of the use of Topicort Topical Spray in patients (b) (4) younger than 18 years of age have not been studied; therefore use in pediatric patients (b) (4) -B (b) ecause of a higher ratio of (b) (4) -skin surface area to body- (b) (4) mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children. [*see Warnings and Precautions (5.1)*]

(b) (4) (HPA) (b) (4) suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in (b) (4) children receiving topical corticosteroids. Manifestations of adrenal suppression in (b) (4) children include (b) (4) low plasma cortisol levels, and absence of response to ACTH

stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. [*See Warnings and Precautions (5.1)*]).

(b) (4)

8.5 Geriatric Use

Clinical studies of Topicort Topical Spray did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

14 CLINICAL STUDIES

(b) (4)

Two multi-center, randomized, double-blind, vehicle- controlled clinical trials were conducted in 239 subjects aged 18 years and older with moderate to severe plaque psoriasis of the body. In both trials, randomized subjects applied Topicort Topical Spray or vehicle spray to the affected areas twice daily for 4 weeks. Enrolled subjects had a minimum body surface area of involvement of 10%, a Physician's Global Assessment score (PGA) of 3 (moderate) or 4 (severe).

Efficacy was assessed at Week 4 as the proportion of subjects who were considered a Clinical Success ("clear" (0) or "almost clear" (1) according to the PGA scale).Table 2 presents the efficacy results.

(b) (4)

Table 2. Number of Subjects (%) with Clinical Success (scored as clear or almost clear) at Week 4.

Parameter	Trial 1		Trial 2	
	Topicort N=59	Vehicle N=60	Topicort N=60	Vehicle N=60
Clinical Success	18(30.5%)	3 (5.0%)	32 (53.3%)	11(18.3%)

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

Inform (b) (4) patients of the following (b) (4)

- Use (b) (4) this medication (b) (4) as directed by the physician.
- Topicort Topical Spray (b) (4) for external use only. Avoid (b) (4) use on the face, axilla or groin.
- (b) (4) Do not to use this medication for any disorder other than that for which it was prescribed.
- Do not bandage (b) (4) or otherwise cover (b) (4) or wrap (b) (4) the treated skin so as to be occlusive (b) (4)
- (b) (4) Report any signs of local or systemic adverse reactions to the physician (b) (4)
- Do not use other corticosteroid-containing products (b) (4) with (b) (4) Topicort Topical Spray, (b) (4) without first consulting with the physician.
- (b) (4) Discontinue (b) (4) therapy when control is achieved. If no improvement is seen within 4 weeks, contact the physician

- This medication is flammable; avoid heat, flame, or smoking when applying this product.
- Discard this product 30 days after dispensed by pharmacist.

Patient Package Insert

Karen Dowdy, RN, BSN, Patient Labeling Reviewer from the Division of Medical Policy Programs (DMPP) reviewed the Patient Package Insert (PPI) and Instructions for Use (IFU). Refer to the review dated 1/11/2013. Lynn Panholzer, PharmD, Regulatory Review Officer from the Division of Professional Drug Promotion (OPDP) reviewed the Patient Package Insert (PPI) and Instructions for Use (IFU) as well as package insert (PI) and carton/container labeling for desoximetasone Spray, 0.25%. Refer to review dated 1/15/2013.

Carton and container labels

The CMC Reviewer, Hamid R. Shafiei, Ph.D. (Review dated 1/23/2013), and the Safety Evaluator, Carlos M Mena-Grillasca, RPh, (Division of Medication Error Prevention and Analysis, Review dated 1/25/2013) provided recommendations regarding the carton and container labels. Negotiations are in progress.

The CMC Reviewer recommended the following:

Immediate container label:

- Adjust the font size for the established name to at least 50% of the Trade name font size on the bottle labels.
- Correct the product name to "TRADENAME (desoximetasone) Topical Spray, 0.25%" on the bottle labels.
- Change the product descriptor from [redacted] (b) (4) to "clear colorless liquid".
- Add the statement "This medication is flammable; avoid heat, flame, or smoking when applying this product."
- Add "discard this product 30 days after purchase" to the bottle labels
- Add [redacted] (b) (4)
- Delete the direction [redacted] (b) (4)
- Delete reference to "For lot number and expiry date see [redacted] (b) (4)

Carton (secondary container) label:

- Adjust the font size for the established name to at least
- 50% of the Trade name font size.
- Correct the product name to "TRADENAME (desoximetasone) Topical Spray, 0.25%" on the bottle labels.
- Change the product descriptor from [redacted] (b) (4) to "clear colorless liquid".
- Add "discard [redacted] (b) (4) product 30 days after [redacted] (b) (4)" to the carton labels

- Add the statement "This medication is flammable; avoid heat, flame, or smoking when applying this product".
- Add the statement "Keep out of reach of children".
- [redacted] (b) (4)

The Safety Evaluator recommended the following:

A. Proposed Container Labels (all package sizes)
Ensure the text on the container labels appear in a horizontal orientation, instead of a vertical orientation, in relation to the orientation the product will normally be stored, held and used by healthcare providers and patients.

B. Proposed Container Labels and Carton Labeling (all package sizes)
1. Revise the presentation of the established name to ensure that it is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).

2. Select another color scheme for the spray formulation that is not currently utilized for another product in any of the Topicort product line.

3. Revise the presentation of the route of administration statements to appear in title case and increase the prominence of the correct route of administration statement, "For Topical Use Only", by presenting the statement on a separate line above the negative route of administration statement "Not for Oral, Ophthalmic, or Intravaginal Use". Also consider bolding the correct route of administration statement "For Topical Use Only".

C. Proposed Container Labels and Carton Labeling (6 mL only)
Include a statement such as 'Physician sample' or 'Sample' as per CFR 203.38(c).

The OPDP Reviewer recommended the following:

- Add [redacted] (b) (4) to the carton and container labels, or delete "twice daily [redacted] (b) (4)" and [redacted] (b) (4) insert for full prescribing information.

- Add a statement to the container label such as "Use within X days of inserting spray pump," and add an instruction to the pharmacist on the carton label to, for example, "Label with an expiration date of X days after inserting spray pump."

Reviewer comment:
We recommend that the applicant add "Use no longer than 4 weeks" to the carton/container labels per OPDP recommendation. The other OPDP comments duplicate other reviewer recommendations or do not provide necessary information to the carton/container labels.

9.3 Advisory Committee Meeting

The Agency conducted no Advisory Committee Meetings regarding this application.

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/s/

MELINDA L MCCORD
01/30/2013

GORDANA DIGLISIC
01/30/2013

DDDP CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA
NDA 204141
Topicort (desoxymetasone) Spray, 0.25%

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY	X			
1. Identify the general format that has been used for this application, e.g. electronic CTD.	eCTD			
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5. Are all documents submitted in English, or are English translations provided when necessary?	X			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57, current divisional and Center policies, and the design of the development package?	X			
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (*i.e*, Module 2 summaries)?	X			
9. Has the applicant submitted the integrated summary of safety (ISS)?	X			
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11. Has the applicant submitted a benefit-risk analysis for the product?	X			
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505(b)(1)			
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: DSXS 0906 Study Title: A Double-Blind, Vehicle-Controlled, Randomized, Dose-Ranging, Multiple-Site Clinical Study to Evaluate the Efficacy and Safety of Two Desoximetasone Topical Sprays (0.05% & 0.25%) in Patients with Moderate to Severe Plaque Psoriasis Sample Size: 150 Arms: A: 30 patients dosed once a day with 0.05% B: 30 patients dosed twice a day with 0.05% C: 30 patients dosed once a day with 0.25% D: 30 patients dosed twice a day with 0.25%	X			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01 html

E: 15 patients dosed once a day with vehicle F: 15 patients dosed twice-a-day with vehicle Location in submission: 5.3.5.1				
EFFICACY				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1 DSXS 0914 Indication: topical treatment of plaque psoriasis Study Population: 120 subjects age 18 years and above Pivotal Study #2 DSXS 0808 Indication: topical treatment of plaque psoriasis Study Population: 120 subjects age 18 years and above	X			
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed?	X			Applicant submitted a waiver.
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	X			
OTHER STUDIES				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?			X	
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (*e.g.*, labeling comprehension)?			X	
PEDIATRIC USE				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS				
26. Has the applicant submitted datasets in a format to allow	X			

reasonable review of the patient data?				
27. Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
29. Are all datasets to support the critical safety analyses available and complete?	X			
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	X			
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	X			
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION				
35. From a clinical perspective, is this application fileable? If “no”, please state why it is not?	X			

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

Melinda McCord, M.D.

Reviewing Medical Officer

Gordana Diglisic, M.D.

Clinical Team Leader

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

/s/

MELINDA L MCCORD
07/23/2012

GORDANA DIGLISIC
07/23/2012