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RESEARCH**

*APPLICATION NUMBER:*

**204141Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	February 11, 2013
<b>From</b>	Gordana Diglisic, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	204141
<b>Applicant</b>	Taro Pharmaceuticals USA, Inc.
<b>Date of Submission</b>	Letter date: CDER stamp date: June 12, 2012
<b>PDUFA Goal Date</b>	April 12, 2013
<b>Proprietary Name / Established (USAN) names</b>	Topicort/ desoximetasone
<b>Dosage forms / Strength</b>	Spray, 0.25%
<b>Proposed Indication(s)</b>	Relief of <span style="background-color: #cccccc;">(b) (4)</span> plaque psoriasis on patients 18 year of age and older
<b>Recommended:</b>	<i>Approval</i>

### 1. Introduction

Topicort (desoximetasone) Topical Spray, 0.25%, is a topical drug product for which the applicant seeks approval under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act for the treatment of (b) (4) plaque psoriasis in patients 18 years of age and older. This application is for a new dosage form of desoximetasone.

The active ingredient, desoximetasone, is a synthetic corticosteroid which is currently marketed in the United States (US) in various topical dosage forms (cream, ointment and gel) by Taro Pharmaceuticals U.S.A., Inc.. The cream formulation [Topicort (desoximetasone cream), 0.25%; NDA 17856] was first approved in the US in 1977.

In addition, desoximetasone is currently approved as 0.05% cream (NDA 18309), 0.05% and 0.25% ointment (NDA 18594 and NDA18763), and 0.05% gel (NDA 17586). All of the above products are approved for the “relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses”.

This memo will summarize the findings of the multidisciplinary review team and provide the rationale for my recommended action.

## 2. Background

The applicant opened the IND (101789) for desoximetasone spray, 0.25% on February 28, 2008 with the protocol for a Phase 1 clinical trial (Vasoconstrictor Study - protocol # 0715005). The applicant did not request an End of Phase 2 meeting and did not request a Special Protocol Assessment for the Phase 3 protocols (submitted on July 28, 2010).

During their development program, the applicant interacted with the Agency at only one milestone meeting, the PreNDA meeting held on July 20, 2011.

## 3. CMC/Device

Topicort (desoximetasone) Topical Spray, 0.25% contains desoximetasone as the active ingredient. The drug substance, desoximetasone, USP is a synthetic corticosteroid. Each gram of Topicort Topical Spray 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 (see Table below):

**Quantitative composition for  
Topicort (desoximetasone) Topical Spray 0.25%**

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

Source: CMC Review (Table 6, page 23)

The manufacturing process for this drug product is well controlled and supported by adequate pharmaceutical and manufacturing development studies.

The specification for the drug product release includes testing and acceptance criteria for description, identification, desoximetasone assay, isopropyl alcohol assay, degradation products (impurities), residual solvents, and minimum fill.

The product specification does not include testing and acceptance criteria for bioburden. Since this drug product is non-aqueous and contains 23.4% isopropyl alcohol and (b) (4) mineral oil, it is suggested that this drug product does not promote microbial growth and therefore, bioburden testing is not necessary. In support of the proposed omission of the bioburden testing from the

drug product specification, the applicant has tested various lots of desoximetasone spray 0.25% for total yeasts and molds, total aerobic microbial count, *Pseudomonas aeruginosa* and *Staphylococcus aureus* (USP <61>, <62>) during product release, stability and through the product's proposed shelf-life as a part of pharmaceutical development. No microbial growth has been observed in any of batches tested. Therefore, the proposed drug product specification is deemed acceptable.

The 6-month accelerated (40°C / 75% RH) and 24-month long-term (25°C / 60% RH) stability results from multiple lots of drug product packaged in all packaging configurations indicated this drug product is stable for 24 month when stored at 20 - 25°C. Additionally the stability data indicated that the proposed container closures and packaging configurations provide adequate protection from light. Based on the stability results, the applicant has proposed an expiration dating period of 24 months and storage condition of 20 – 25°C with excursion permitted to 15 – 30°C for the drug product packaged in the proposed container closures. The proposed expiration dating period and storage condition are considered acceptable.

#### Container Closure System:

The proposed container closure system for Topicort Topical Spray is 6-mL (physician sample), (b) (4) 30-mL, 50-mL, and 100-mL white high-density polyethylene (HDPE) round bottles with white (b) (4) screw cap closures accompanied with a (b) (4) manual spray pump with screw type closure. The spray pump is to be installed by the pharmacist prior to dispensing to patients. Based on the pump performance and 28-day in-use stability data as well as the risk-based assessment of the potential leachables / extractables, the proposed container closures are compatible with the drug product.

The CMC reviewer concluded that the applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.

Recommendation from the Office of Compliance regarding facilities inspections for the drug substance and drug product is pending.

The reader is referred to the comprehensive review by Hamid R. Shafiei, Ph.D; Office of New Drug Quality Assessment; Division of New Drug Quality Assessment II, Branch IV; dated 01/23/13.

## 4. Nonclinical Pharmacology/Toxicology

In addition to the toxicology studies submitted within NDA17856 (Topicort Cream) , NDA18763 (Topicort Ointment), and NDA18568 (Topicort Gel) of which the applicant has ownership, the applicant submitted 28-day repeat dose dermal toxicity bridging study in minipigs conducted with desoximetasone spray and cream, 0.25%, an ICH standard battery of genetic toxicology studies and a subcutaneous fertility study in rats.

From Pharmacology/Toxicology review:

General Toxicology and Pharmacokinetics/Toxicokinetics

“Following 28 days of dermal administration of desoximetasone spray, 0.25% and desoximetasone cream, 0.25% to Göttingen minipigs at the same daily dose level of 0.33 mg/kg, no significant differences in toxicological profile were revealed. The signs of toxicity observed were decreases in adrenal weights and reversible atrophic changes in the adrenal gland and/or thymus, which were present in all treated groups. These observations are consistent with results from previous repeat dose toxicity studies and are known pharmacological effects of desoximetasone, resulting from the HPA axis suppression. Signs of application site irritation were no more frequent in desoximetasone treated groups than in vehicle control group. Toxicokinetic analysis demonstrated that dermal administration of desoximetasone spray, 0.25% resulted in greater systemic exposure to active drug than desoximetasone cream, 0.25% ( $C_{max}$  and  $AUC_{0-24}$  values were approximately 2-fold greater for the spray formulation). There are no clear gender differences in TK parameters within a dose or formulation.”

Genetic toxicology

“Desoximetasone revealed no evidence of mutagenic or clastogenic potential 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).”

Carcinogenicity

“Long-term animal studies have not been performed to evaluate the carcinogenic potential of desoximetasone. The sponsor committed to conduct a 2 year dermal carcinogenicity study in rats as a post-marketing requirement.”

Reproductive toxicology

“No evidence of impairment of fertility was observed in male and female Sprague-Dawley rats by subcutaneous doses up to 0.1 mg/kg/day desoximetasone.

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Desoximetasone has been shown to be teratogenic and embryotoxic in mice, rats, and rabbits when given by subcutaneous or dermal routes of administration in doses 3 to 30 times the human dose of Topicort (desoximetasone cream USP) 0.25% and 15 to 150 times the human dose of Topicort (desoximetasone cream USP) 0.05%, or Topicort (desoximetasone gel USP) 0.05%.”

Impurities/excipients

“Desoximetasone spray, 0.25% does not contain any novel excipients. None of the impurities in the drug substance are above the ICH qualification threshold. Impurities (b) (4) in the

proposed drug product are above the ICH qualification threshold. However, there are no concerns from a pharmacology/toxicology perspective based on the nonclinical data and justification the sponsor provided.”

The reader is referred to the comprehensive review by Dr. Renqin Duan for a full discussion of the nonclinical pharmacology/toxicology data (dated 01/07/13).

Drs. Renqin Duan and Barbara Hill recommended an *Approval* of this application pending agreements on the recommended labeling changes. However, since long-term animal studies have not been performed to evaluate the carcinogenic potential of desoximetasone, the Pharmacology/Toxicology Team recommend a Post-marketing Requirement:

- A two year dermal carcinogenicity study in rats.

The applicant intends to conduct 28 and 90 day dose range finding studies to determine the appropriate maximum tolerated dose to be used in this two 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 proposed timeline: Submission of Final Study Protocol: April 2015; Completion of 2-year rat study: May 2017; Submission of Final Study Report: May 2018. (Pharmacology/Toxicology Review dated 01/07/13)

## 5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted two clinical pharmacology studies:

- Vasoconstriction Assay (VCA) study (10715005), and
- Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression study (DSXS-0805)

### Vasoconstriction Assay (VCA)

A vasoconstriction study was conducted in 32 healthy adult subjects to determine the relative vasoconstrictive potency of Topicort Topical Spray, 0.25% compared to a placebo spray (vehicle), and seven other marketed corticosteroid formulations of known potency. The degree of vasoconstriction was evaluated using single timepoint visual scoring as well as using a single timepoint ChromaMeter (a-scale reading) assessment two hours after product removal.

Based on the visual scoring data, the skin blanching response of Topicort Topical Spray, 0.25% was not significantly different from clobetasol propionate 0.05% spray (Class 1), mometasone furoate 0.1% ointment (Class 2), desoximetasone 0.25% cream (Class 2), and fluocinonide 0.05% ointment (Class 2), and was significantly different from fluticasone propionate 0.05% cream (Class 5), and hydrocortisone 2.5% cream (Class 7).

Therefore, 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.

Effect on the Hypothalamic-Pituitary-Adrenal (HPA) Axis:

Study DSXS-0805 was an open label study to assess the potential of Topicort (desoximetasone) Topical Spray, 0.25% to suppress HPA axis function in 24 subjects 18 years of age and older with moderate to severe plaque psoriasis [Physician's Global Assessment (PGA) score of 3 or 4]. Subjects were enrolled in 2 cohorts: 12 subjects with involvement of 10-15% of their body surface area (BSA) and 12 subjects with involvement of > 15% of their BSA. Topicort Topical Spray was applied to the affected areas twice daily for 28 days.

Twenty-one subjects had evaluable serum cortisol levels and the proportion of subjects demonstrating HPA axis suppression was 8.3% (1 out of 12) in subjects having involvement of 10-15% of BSA, and 22.2% (2 out of 9) in subjects having involvement of > 15% of their BSA. In this study HPA axis suppression was defined as serum cortisol level  $\leq$ 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.

Pharmacokinetics:

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

Clinical Pharmacology Team Labeling Recommendations:

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

**5.1 Effect on Endocrine System**

(b) (4)

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

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

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

(b) (4)

(b) (4)

(b) (4)

### **12.2 Pharmacodynamics**

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

(b) (4)

(b) (4)

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

### **12.3 Pharmacokinetics**

...Plasma concentrations of desoximetasone were measured at two single random time points in (b) (4) the HPA axis suppression trial (b) (4) in

24 subjects with psoriasis. The mean (% Coefficient of Variation) concentration of desoximetasone was 449 pg/mL (86%) at Day 14 and 678 pg/mL (135%) at Day 28. The concentration time profile following application of Topicort Topical Spray is not known. (b) (4)

(b) (4)

The reader is referred to the comprehensive review by An-Chi Lu, Ph.D. for a full discussion of the clinical pharmacology data (dated 01/18/13).

The clinical pharmacology reviewer, Dr. An-Chi Lu, recommended *Approval* of this application “pending agreement on recommended labeling changes and the post marketing requirements outlined in section 1.2 of this review.

### **1.2 Phase IV Commitments/Requirements**

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

Cohort 1: age 12 years to 16 years 11 months

Cohort 2: age 6 years -11 years and 11 months

Cohort 3: age 2 years to 5 years and 11 months”

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical- Efficacy**

The applicant submitted data from two pivotal trials, DSXS-0808 and DSXS-0914, to establish the effectiveness of their product applied twice daily for 28 days in the treatment of plaque psoriasis.

Trials DSXS-0808 and DSXS-0914 were multicenter (9 centers/trial in the U.S.), randomized, double-blind, vehicle-controlled, parallel-group Phase 3 trials. The population enrolled was subjects 18 years of age and older with a stable plaque psoriasis involving  $\geq 10\%$  of the body surface area (BSA). In addition, inclusion criteria include a sore of moderate (3) or severe (4) on the PGA scale, target lesion area at least 5 cm<sup>2</sup> (not on the face, genitals or intertriginous area), a sore of  $\geq 7$  for the target lesion on Total Lesion Severity Scale (TLSS), and Plaque elevation score  $\geq 3$ . Subjects with plaque psoriasis of the scalp/face requiring the treatment during the trial were excluded. In those trials, safety and efficacy of the Topicort (desoximetasone) Topical Spray, 0.25% was evaluated in comparison to vehicle. Eligible subjects were randomized to one of the following treatments in a 1:1 ratio: (1) Topicort Topical Spray and (2) Vehicle Spray. Subjects were evaluated at Day 7, 14, and 28.

A total of 240 were enrolled [120 in the desoximetasone arm (one subject did not have a post-baseline evaluation) and 120 in vehicle arm]. Both trials were fairly evenly balanced across treatment arms in terms of age, however, in both trials, more male subjects (66% in the desoximetasone arm and 65% in the vehicle arm) than female subjects were enrolled. The majority of subjects were white in both trials (96% in the desoximetasone arm and 94% in the vehicle arm). At baseline, about 70% of the subjects were graded as “moderate” on the PGA scale (i.e., PGA=3) with the mean percentage of BSA affected of about 16.

A total of 24 subjects withdrew from the Phase 3 trials (9.2% in the Topicort Topical Spray arm; 10.8% in the vehicle arm). The most common reason for withdrawal was “change in scheduled visit” followed by “patient ran out of the study medication” in the Topicort Topical Spray arm and “change in scheduled visit” followed by “adverse event-psoriasis” in the vehicle arm.

The protocol specified co-primary efficacy endpoints were the following:

- proportion of subjects who were a Clinical Success (PGA score of 0 or 1) at Day 28
- proportion of subjects who were a Treatment Success for the Target Lesion (a score of 0 or 1 for each of the three signs, i.e., erythema, scaling and plaque elevation) at Day 28.

The efficacy analysis was based on the Intent to Treat (ITT) population (defined as all randomized subjects who had at least one post-baseline assessment).

Summary of co-primary efficacy results is given in the following table.

	<b>(desoximetasone), Topical Spray, 0.25%</b>	<b>Vehicle</b>	<b>p-value<sup>(3)</sup></b>
<b>Study 0808</b>			
Clinical Success <sup>(1)</sup>	18/59 (30.5%)	3/60 (5.0%)	0.0003
Treatment Success <sup>(2)</sup>	23/59 (39.0%)	4/60 (6.7%)	<0.0001
<b>Study 0914</b>			
Clinical Success <sup>(1)</sup>	32/60 (53.3%)	11/60 (18.3%)	<0.0001
Treatment Success <sup>(2)</sup>	32/60 (53.3%)	10/60 (16.7%)	<0.0001

(1) Clinical success is defined as having PGA of 0 or 1 at Day 28

(2) Treatment success is defined as having signs and symptoms of score 0 or 1.

(3) P-value is calculated from two-sided continuity corrected Z test.

Source: applicant’s analysis.

As a sensitivity analysis, statistical reviewer considered the worst case scenario and imputed the missing data in the vehicle arm as successes, and the missing data in the desoximetasone arm as failures. Even under such worst case scenario, both Phase 3 trials (DSXS-0808 and DSXS-0914) met the statistical significance level of 0.05 for the co-primary endpoints (see Table below).

	<b>(desoximetasone), Topical Spray, 0.25%</b>	<b>Vehicle</b>	<b>p-value<sup>(3)</sup></b>
<b>Study 0808</b>			
Clinical Success <sup>(1)</sup>	18/59 (30.5%)	9/60 (15.0%)	0.043
Treatment Success <sup>(2)</sup>	23/59 (39.0%)	9/60 (15.0%)	0.003
<b>Study 0914</b>			
Clinical Success <sup>(1)</sup>	31/60 (51.7%)	17/60 (28.3%)	0.009
Treatment Success <sup>(2)</sup>	32/60 (53.3%)	17/60 (28.3%)	0.005

(1) Clinical success is defined as having PGA of 0 or 1 at Day 28

(2) Treatment success is defined as having signs and symptoms of score 0 or 1.

P-value is calculated from Chi-square test.

Source: statistical reviewer's analysis (Table 9); addendum dated 02/12/13

It appears that there is no differential treatment effect by gender or age, although the proportion of subjects with clinical success appears to be higher for those >65 years of age, it should be noted that the majority of the subjects were ≤65 years of age.

In terms of the baseline PGA score, about 70% of the subjects who entered the trial had a baseline PGA score of 3 (moderate), and the treatment effect for the Clinical Success is about 30% for these subjects in both trials. For the subjects who entered the trial with a PGA of 4 (severe), while DSXS-0808 showed that the treatment effect is only about 13.3%, results from DSXS-0914 show that the treatment effect for the Clinical Success is about 45%. However, because the number of subjects in this severity group is relatively small, it is difficult to draw any reasonable inference.

The target lesions of most subjects who entered the trials had moderate erythema, moderate scaling, and moderate plaque elevation. Because the number of subjects in other severity groups is too small, it is difficult to draw any reasonable inference. For the TLSS, those subjects with scores of 7-9 had higher Treatment Success compared to those with scores of 10-15.

In summary, the applicant has established the efficacy of their product in the treatment of plaque psoriasis of the body.

The reader is referred to the comprehensive statistical review and evaluation by Carin J Kim, Ph.D. (Division of Biostatistics III) for a more complete discussion of the efficacy results (dated 01/16/13).

## 8. Safety

The applicant submitted data from two Phase 3 trials (DSXS-0808 and DSXS-0914) and one supportive Phase 2 trial (DSXS-0906). The trials are summarized in Table below:

Protocol	Study Design/Type of study	Subject Population	Test products/ Dosage regimen	Enrollment	Treatment duration
<b>DSXS-0808 (Phase3)</b>	Double-blind, vehicle-controlled, randomized, parallel group/  Safety and efficacy	≥ 18 years moderate to severe plaque psoriasis involving 10% BSA	desoximetasone spray, 0.25%/bid	120	28 days
			vehicle spray/bid	60	
				60	
<b>DSXS-</b>	Double-blind, vehicle-controlled, randomized,	≥ 18 years moderate to severe plaque	desoximetasone	120	28 days
				60	

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<b>0914 (Phase3)</b>	parallel group/ Safety and efficacy	psoriasis involving 10% BSA	spray, 0.25%/bid  vehicle spray/bid	60	
<b>DSXS-0906 (Phase2)</b>	Double-blind, vehicle- controlled, randomized, parallel group/  Dose ranging/Safety and efficacy	≥ 18 years moderate to severe plaque psoriasis involving 10% BSA	desoximetasone spray, 0.25%/qd  desoximetasone spray, 0.25%/bid  desoximetasone spray, 0.05% /gd  desoximetasone spray, 0.05% /bid  vehicle spray /qd  vehicle spray /bid	30*  29  30*  31*  15*  15	28 days

\*Not included in pooled safety database

A total of 240 subjects were enrolled in Phase 3 trials and 120 subjects were exposed to Topicort (desoximetasone) Topical Spray, 0.25%. Safety data from the pivotal trials have been integrated with safety data from the supportive trial (DSXS-0906). However, subjects who were exposed to Topicort Topical Spray 0.25% once daily, vehicle spray once daily or to Topicort Topical Spray 0.05% once or twice daily were not included in pooled safety database as the dose and/or dose regimen differs from the Phase 3 trials and proposed product labeling. Therefore, from a total of 151 subjects enrolled in Phase 2 trial, 29 subjects were exposed to Topicort Spray 0.25% bid and 15 subjects were exposed to vehicle spray bid. There were 36 subjects who participated in the Phase 2 trial (DSXS-0906) and one of the Phase 3 trials. The interval between treatments (from Phase 2 to Phase 3 trial) was greater than 148 days.

The integrated/pooled safety database includes 284 subjects: 149 exposed to Topicort (desoximetasone) Topical Spray, 0.25% bid and 135 exposed to vehicle spray bid. Subjects were to have applied study product to the affected areas on the body twice daily for 28 days. The amount applied was not recorded. Safety was assessed by adverse events (Day 7, 14 and 28), and vital signs (blood pressure, pulse, temperature, and respiration rate). Vital signs were assessed at baseline and at the end of the treatment (Day 28). Laboratory assessments were not performed during these trials. The mean ( $\pm$  SD) duration of exposure was  $27.7 \pm 4.3$  days for subjects treated with Topicort Topical Spray.

There were no deaths reported, and no serious adverse events (SAE) attributable to Topicort (desoximetasone) Topical Spray, 0.25%.

Overall, 1.8% (5/284) of subjects discontinued from trials due to adverse events. The adverse events resulting in subject discontinuation in the Topicort Topical Spray arm were pruritus and psoriasis (reported by one subject). Four subjects in the vehicle arm reported application site burning (one subject), application site dryness and itching (one subject), application site erythema (one subject), and application site stinging and worsening of psoriasis (one subject) which led to discontinuation from the trials.

A total of 55 adverse events (AEs) were reported by 29 subjects (29/149; 19%) in the Topicort Topical Spray arm. The most frequent treatment-emergent adverse events in the Topicort Topical Spray arm were application site irritation (2.7%), application site dryness (2.7%), and headache (2.7%), application site pruritus (2.0%) and folliculitis (1.3%). In the vehicle arm, the most frequent treatment-emergent adverse events were application site dryness (5.2%), application site irritation (3.7%), application site pruritus (3.7%), headache (2.2%), application site erythema (1.5%), and application site pain (1.5%). Regarding the AE – headache, review of case report forms indicates the event is unlikely to be related to study drugs. Most events were mild or moderate in intensity. Severe AEs were reported by three subjects: Topicort Topical Spray group (2/149) and one in the vehicle group. In the Topicort Topical Spray group, one subject reported application site pruritus (0.7%) and one skin ulcer (not at the application site; 0.7%). In the vehicle group, one subject reported application site erythema (0.8%).

The most frequently reported adverse reactions (ARs) in subjects treated with Topicort Topical Spray were related to the application site: dryness and irritation (2.7%), followed by application site pruritus (2.0%). Another less common adverse reaction (<1% but >0.1%) was folliculitis.

Collection of adverse event data, assessment of local tolerance and vital signs evaluation did not reveal unexpected safety signals.

The applicant conducted 3 dermal safety trials in population of healthy subjects to evaluate the cumulative skin irritation and sensitization (DSXS-0804), phototoxicity (DSXS-0904) and photoallergenicity (DSXS-0905) potential of Topicort Topical Spray, 0.25%. The findings from those trials support the conclusion that Topicort Topical Spray, 0.25% has limited potential to induce skin irritation and sensitization. Additionally, none of the subjects experienced phototoxicity or photoallergic skin reactions.

#### Special safety concern

HPA axis suppression is a special safety concern with this drug product.

In trial DSXS-0805, HPA axis suppression was evaluated in adult subjects (N=24) with psoriasis involving  $\geq 10\%$  BSA. Adrenal suppression was identified in 1 out of 12 subjects

having involvement of 10-15% of BSA and 2 out of 9 subjects having involvement of >15% of BSA after treatment with Topicort Topical Spray twice a day for 28 days.

The reader is referred to the Section 5 (Clinical Pharmacology) of this review and to the reviews by An-Chi Lu, Ph.D. and Melinda McCord, MD, for full discussion.

The 120-day safety update was reviewed, and did not identify new safety signals.

The reader is referred to the clinical review by Dr. Melinda McCord, MD for discussion of the safety database (01/30/13)

No postmarketing commitments or requirements to address safety concerns (outside of PREA) are warranted.

## 9. Advisory Committee Meeting

Not applicable, as no Advisory Committee meeting was held for this application.

## 10. Pediatrics

In the support of current submission, the applicant conducted Phase 3 trials in subjects 18 years of age and older with plaque psoriasis.

The applicant requested a pediatric waiver

(b) (4)

Based on the epidemiology of psoriasis in the pediatric population and because of a higher ratio of skin surface area to body mass, young children (<2 years of age) are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. Therefore, a partial waiver in pediatric patients less than 2 years of age is reasonable. It is recommended that the pediatric study requirements for pediatric patients ages 0-2 years of age, be waived because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric age group.

However, given the lack of HPA axis suppression data in the pediatric population 2-17 years of age, and the risk/benefit assessment posed by alternative therapies, the applicant was asked to submit a revised pediatric plan to address the above issues. The reader is referred to the review from the Pediatric and Maternal Health Staff (by Elizabeth Durmowicz, MD and Hari

Sachs, MD; Consult dated 12/3/12), and review from the Division of Metabolism and Endocrinology Products (by Ali Mohamadi; Consult dated 12/5/12).

Establishment of the safety of Topicort Topical Spray for the treatment of pediatric subjects 2-17 years with plaque psoriasis would require an understanding of the systemic exposure and systemic safety of that exposure. Therefore, an additional trial is needed to establish the safety of Topicort (desoximetasone) Topical Spray, 0.25% in this pediatric population for the treatment of plaque psoriasis.

Such a trial should be conducted in approximately 100 evaluable subjects age 2-16 years and 11 months with plaque psoriasis to evaluate the safety and effect of Topicort Topical Spray, 0.25% on HPA axis and the pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment. The trial should be conducted in sequential cohorts (Cohort 1: age 12 years to 16 years 11 months; Cohort 2: age 6 years to 11 years and 11 months; Cohort 3: age 2 years to 5 years and 11 months). Safety assessments should also include: vital signs, physical examinations, local safety, and adverse events.

The applicant submitted a revised Pediatric Development Plan with a request for partial waiver for pediatric patients 0-2 years of age (the drug product would be unsafe in this pediatric age group), and a request for deferral of pediatric study for pediatric patients 2-16 years and 11 months of age (including proposed dates for final protocol submission, trial initiation, and final report submission).

The application was presented to the Pediatric Review Committee (PeRC) on January 9, 2013. The committee agreed with the proposed Pediatric Development Plan.

## **11. Other Relevant Regulatory Issues**

A total of two investigator sites were inspected in support of this NDA. No deficiencies were found that would preclude reliance upon the data that was submitted. The reader is referred to the Clinical Inspection Summary by Roy Blay, Ph.D.; Good Clinical Practice Assessment Branch; Division of Good Clinical Practice Compliance; Office of Scientific Investigations; dated 12/26/12.

## **12. Labeling**

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding their content are ongoing at the time of close of this review.

By letter dated November 7, 2012, the applicant requested a review of a proposed proprietary name, Topicort. On February 4, 2013 the Division of Medication Error Prevention and Analysis completed their review of the proposed proprietary name and concluded that it is acceptable.

Because 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.

Significant changes incorporated into revised draft labeling, following labeling review, include

- **5 WARNINGS AND PRECAUTIONS;**  
**5.1 Effects on Endocrine System** – see Section 5 of this review;  
**5.5 Flammable Contents**  
Topicort Topical Spray is flammable; keep away from heat or flame
- **12 CLINICAL PHARMACOLOGY; 12.1 Mechanism of Action; 12.2 Pharmacodynamics; 12.3 Pharmacokinetics** – see Section 5 of this review

### **13. Recommendations/Risk Benefit Assessment**

Recommended Regulatory Action: *Approval*

- I concur with the recommendations of the multi-disciplinary review team for approval of NDA 201141, Topicort (desoximetasone) Topical Spray, 0.25% pending agreement of the applicant with the recommended labeling revisions and the recommendation from the Office of Compliance regarding facilities inspections for the drug substance and drug product

Risk Benefit Assessment

- The risk-benefit assessment supports approval of this product for the treatment of plaque psoriasis in patients 18 years of age and older

Recommendation for Postmarketing Risk Evaluation and Management Strategies

- Postmarketing risk management beyond professional labeling, prescription status and routine pharmacovigilance is not needed.

Recommendation for other Postmarketing Requirements and Commitments

1. To fulfill the requirements of PREA, the applicant will need to:

Conduct a trial in 100 evaluable pediatric subjects with plaque psoriasis of the body ages 2-16 years and 11 months. Evaluate the safety and effect of Topicort (desoximetasone) Topical Spray, 0.25% on the hypothalamic-pituitary axis and the pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment. The trial should be conducted in sequential cohorts

Cross Discipline Team Leader Review  
NDA 204141  
Topicort (desoximetasone) Topical Spray, 0.25%

Cohort 1: age 12 years to 16 years 11 months  
Cohort 2: age 6 years to 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

2. A two year dermal rat carcinogenicity study

Final Study Protocol: 04/30/15  
Study Completion: 05/31/17  
Final Study Report: 05/31/18

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GORDANA DIGLISIC  
02/12/2013