Clinical Review and Evaluation

PMR Final Study Report

Application Type	sNDA: Efficacy Supplement
Application Number(s)	NDA 204141/S-009; IND 101789
Priority or Standard	Standard
Submit Date(s)	December 15, 2020
Received Date(s)	December 15, 2020
PDUFA Goal Date	October 15, 2021
Division/Office	Division of Dermatology and Dentistry (DDD) / Office of Immunology and Inflammation
Reviewer Name	K. Dev Verma, MD
Review Completion Date	August 19, 2021
Established Name	Desoximetasone
(Proposed) Trade Name	TOPICORT Topical Spray, 0.25%
Pharmacologic Class	Corticosteroid
Code Name	None
Applicant	Taro Pharmaceuticals
Formulation	Topical Spray
Dosing Regimen	Twice daily
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of plaque psoriasis in patients 18 years of age or older. The Applicant is not seeking expansion to the pediatric population.
Recommendation on Regulatory Action	Approval; PMR 2029-1 Fulfilled
Recommended Indication(s)/Population(s)	For the topical treatment of plaque psoriasis in patients 18 years of age or older

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1. Executive Summary

TOPICORT® (desoximetasone) Topical Spray, 0.25% is a corticosteroid indicated for the treatment of plaque psoriasis in patient 18 years of age or older. TOPICORT Topical Spray, 0.25% was approved April 11, 2013.

The active ingredient, desoximetasone, is a synthetic corticosteroid which is currently marketed in the United States (US) in various topical dosage forms (cream, ointment, gel, and spray) 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.

At the time of approval of TOPICORT Topical Spray, 0.25% in 2013, given this was a new dosage form of desoximetasone, the Pediatric Research Equity Act (PREA) was triggered. The Approval Letter on April 11, 2013 required the Applicant to conduct a deferred study under PREA PMR:

> "We are waiving the pediatric study requirement for ages 0 years to 1 year 11 months because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric group.

> We are deferring submission of your pediatric study for ages 2 years to 16 years 11 months for this application because this product is ready for approval for use in adults and the pediatric study has not been completed
>
> PMR 2029-1:
> Conduct a trial in 100 evaluable pediatric patients with plaque psoriasis ages 2 to 16 years and 11 months. Evaluate the safety and effect of Topicort (desoximetasone) Topical Spray, 0.25% on the hypothalamic-pituitary-adrenal axis and pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment. Conduct the trial in sequential cohorts, for example:
>
> 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"

The labeling for TOPICORT Topical Spray, 0.25% carries the following Warnings and Precautions: "Topicort® Topical Spray can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency during or after treatment. Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can result from systemic absorption of topical corticosteroids. Because of the potential for systemic absorption, use of topical corticosteroids may require that patients be periodically evaluated for HPA axis suppression. Modify use if HPA axis suppression develops. High potency corticosteroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure and young age may predispose patients to HPA axis suppression. Pediatric patients may be more susceptible to systemic toxicity when treated with topical corticosteroids. Topicort® Topical Spray is flammable; keep away from heat or flame."

To address PREA PMR 2029-1, the Applicant conducted Trial DSXS-1303, and submitted an efficacy Supplemental NDA (sNDA) S-009, without seeking expansion of the indication to the pediatric population. Trial DSXS-1303 was conducted to evaluate the safety and effect of TOPICORT Topical Spray, 0.25% on the hypothalamic-pituitary-adrenal axis (HPA) axis, and pharmacokinetics (PK) of desoximetasone under maximal use conditions after 4 weeks of treatment. In addition, the Applicant submitted proposed labeling which is compliant with the Pregnancy and Lactation Labeling Rule (PLLR).

Trial DSXS-1303 was an open-label, safety, and pharmacokinetic trial enrolling 129 subjects 2 to less than 18 years of age with moderate to severe plaque psoriasis who were treated with TOPICORT Topical Spray, 0.25% under maximal use conditions. The proportion of subjects demonstrating HPA axis suppression was 35.0% (21 out of 60) in Cohort 1 (12 years to less than 18 years of age, with a mean baseline BSA involvement of 16%), 43.3% (13 out of 30) in Cohort 2 (6 years to less than 12 years of age, with a mean baseline BSA involvement of 19%) and 20.0% (2 out of 10) in Cohort 3 (2 years to less than 6 years of age, with a mean baseline BSA involvement of 16%). Adrenal suppression was reversable in 80.6% (29 out of 36) of subjects upon retesting at least 4 weeks after treatment cessation (however, 7 subjects were lost to follow up or refused follow up testing). A single subject (1 out of 129, 0.8%) experienced a

headache, and this subject also had HPA axis suppression. No other safety signals (local or systemic) were identified during this trial.

This reviewer recommends that PMR 2029-1 be considered fulfilled, and the indication for TOPICORT Topical Spray, 0.25% should not be expanded to the pediatric population due to the high incidence of HPA axis suppression observed from this trial in the pediatric population. As the labeling review is still in progress, this recommendation is contingent upon the successful completion of labeling negotiations with the Applicant.

1.1. Benefit-Risk Assessment

In this supplement, the Applicant submitted results from open-label Trial DSXS-1303 to provide safety (local and systemic safety, including effect on the HPA axis), and PK data for TOPICORT Topical Spray, 0.25% for the topical treatment of pediatric subjects 2 to less than 18 years of age with moderate to severe plaque psoriasis. A total of 129 subjects with moderate to severe plaque psoriasis, defined as a Physician Global Assessment (PGA) score of 3 (moderate) or 4 (severe) and at least 10% total body surface area (BSA) affected, applied TOPICORT Topical Spray, 0.25% twice daily for 4 weeks. A total of 1 subject experienced 1 adverse event (AE), of mild headache. This AE was possibly related to the study product and this subject also met biochemical criteria for HPA axis suppression. The overall rate of HPA axis suppression was found to be greater in the pediatric population (36%) compared to the adult population (14%). Of the 36 subjects with HPA axis suppression, HPA axis suppression ultimately resolved in 29 subjects (80.6%) after treatment cessation. However, the other 7 subjects were lost to follow up or refused follow up testing, therefore the true incidence of HPA axis suppression resolution in this trial is unclear. Although the trial did not primarily evaluate efficacy, (b) (4) .

Based on the number of subjects who developed HPA axis suppression during this clinical trial in the pediatric population, an unfavorable benefit-risk conclusion is indicated, and therefore the use of TOPICORT Topical Spray, 0.25% is not recommended to the pediatric population.

2. Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, immune-mediated skin disorder which may develop in genetically susceptible individuals.[1] Chronic plaque psoriasis is the most common form of psoriasis in children and adults.[2] Other forms of psoriasis include guttate, pustular, and erythrodermic psoriasis. The characteristic lesion is a sharply demarcated, erythematous plaque with

[1] Mallbris L et al. J Invest Dermatol. 2005 Mar;124(3):499-504.
[2] Paller AS et al. Psoriasis in children: Epidemiology, clinical manifestations, and diagnosis. UpToDate. Accessed March 22, 2021.

micaceous scale; the plaques may be localized or widespread in distribution. Common sites of involvement are scalp, elbows, knees, and presacral region. However, psoriasis may occur on any cutaneous site including the palms, soles, nails, and genitalia.[3] The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, producing proinflammatory cytokines which trigger and perpetuate the inflammatory cascade.

The prevalence of psoriasis varies by geographic region. The estimated prevalence worldwide ranges from 0 to 1.37% of children and 0.51 to 11.3% of adults.[4] Studies of the United States population found prevalence rates of up to 4.6%.[2] Among the estimated 7.5 million Americans affected with psoriasis, 80% have mild to moderate disease, while 20% have moderate to severe disease affecting more than 5% of the body surface area.[5]

The onset of psoriasis may occur at any age, but often occurs in childhood. The reported median age of onset of childhood-onset psoriasis is between 7 and 10 years.[6] In approximately 35–50% of individuals, psoriasis develops before the age of 20 years; in approximately 75% of individuals, psoriasis develops before the age of 40 years.[2] Regardless of the age of onset, psoriasis is characterized by a chronic course with intermittent remissions.

The areas of involvement and presentation of psoriasis may vary with age. In infants, psoriasis often presents with symmetrical, well-demarcated, thin, erythematous plaques with minimal scale in the diaper area. In children, psoriasis commonly presents on the scalp and may involve the face.[7,8] In all age groups, psoriasis is associated with an increased risk of a number of comorbid conditions including obesity, cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, autoimmune disorders, psychiatric and behavioral disorders.[9]

2.2. Analysis of Current Treatment Options

FDA approved products available for the treatment of plaque psoriasis in the pediatric population are outlined in Table 1. FDA approved topical treatments for psoriasis in the pediatric population include: TACLONEX® (calcipotriene and betamethasone dipropionate) ointment and topical suspension, 0.005%/0.064%, a combination vitamin D analog and corticosteroid indicated for the topical treatment of plaque psoriasis of the scalp and body in patients 12 years and older; VECTICAL® (calcitriol) ointment, a vitamin D analog indicated for the topical treatment of mild to moderate plaque psoriasis patients 2 years and older; OLUX-E®

[3] Shah KN. Diagnosis and treatment of pediatric psoriasis: current and future. Am J Clin Dermatol. 2013;14(3):195.
[4] Michalek IM et al. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017;31(2):205.
[5] Menter et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008; 58(5):826-50.
[6] Raychaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. Pediatr Dermatol. 2000;17:174-178.
[7] Morris A et al. Childhood psoriasis: a clinical review of 1262 cases. Pediatr Dermatol. 2001;18(3):188.
[8] Mercy K et al. Clinical manifestations of pediatric psoriasis: results of a multicenter study in the United States. Pediatr Dermatol. 2013 Jul;30(4):424-8.
[9] Elmets et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol 2019; 80:1073-113.

(clobetasol propionate) Foam, 0.05%, a Class I high potency corticosteroid indicated for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years and older; DIPROLENE® (augmented betamethasone dipropionate) ointment, 0.05%, a Class I high potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years and older; VANOS® (fluocinonide) cream, 0.1%, a Class II high potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in patients 12 years and older; and TAZORAC® (tazarotene) gel, 0.05% and 0.1%, a retinoid indicated for the topical treatment of plaque psoriasis of up to 20% body surface area involvement in patients 12 years and older.

FDA approved systemic treatments for psoriasis in the pediatric population include: ENBREL® (Etancerpt), a TNF blocker indicated for the treatment of patients 4 years or older with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy; and STELARA® (ustekinumab), a human interleukin-12 and -23 antagonist indicated for the treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Other topical therapies used in clinical practice as off-label first-line agents for mild to moderate psoriasis in pediatric patients include: low potency short-term topical corticosteroids, anthralin, calcipotriene, salicylic acid, calcineurin inhibitors, and coal tar.[10] Phototherapy and systemic medications are typically reserved for extensive or refractory disease.

In 2013, the FDA approved TOPICORT Topical Spray, 0.25% for the treatment of plaque psoriasis in patients 18 years of age or older. Desoximetasone, a Class I/II corticosteroid, is marketed in four formulations (cream, gel, ointment and spray) and two concentrations (0.25% and 0.05%). No desoximetasone drug product marketed in the United States is approved for use in children. Per current labeling of topical desoximetasone products, adverse reactions resulting from systemic absorption of topical corticosteroids include: 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.

Of note, 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.[11] Adverse reactions observed in pediatric patients exposed to topical corticosteroids include: HPA axis suppression, Cushing's syndrome, and

[10] Eichenfield et al. Pediatric psoriasis: Evolving Perspectives. Pediatr Dermatol. 2018;35:170-81.
[11] Pediatric Use Sections of current labeling of desoximetasone ointment, cream, gel and spray.

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. Many other marketed Class I/II topical steroids are not specifically approved in pediatric patients but include a statement in pediatric use recommending that "administration of topical corticosteroids in pediatric patients be limited to the least amount compatible with an effective therapeutic regimen."

Table 1: Products Available for the Treatment of Plaque Psoriasis in the Pediatric Population

Example Product	Product Class	Indication	Dosage and Administration	Important Safety and Tolerability Issues
Topical Products				
Vectical (calcitriol) ointment	Synthetic Vitamin D3 Derivative	Mild to moderate plaque psoriasis in patients 2 years of age and older	Apply twice daily	Most common adverse reactions (incidence >3%) are hypercalcemia, hypercalciuria, and skin discomfort.
Taclonex (calcipotriene and betamethasone dipropionate) ointment and topical suspension	Synthetic Vitamin D3 Derivative / Corticosteroid Combination Product	Plaque psoriasis in patients 12 years and older	Apply once daily up to 4 weeks; Discontinue when control is achieved	Most common adverse reactions (≥1%) are pruritus and scaly rash. Hypercalcemia and hypercalciuria have been observed. Can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency during and after withdrawal of treatment. May increase the risk of cataract and glaucoma.
Olux-E (clobetasol propionate) foam	Corticosteroid (Class I, high potency)	Treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients aged 12 years and older	Apply twice daily up to 2 weeks	Most common adverse reactions (incidence ≥1%) are application site atrophy and application site reaction. Systemic absorption of Olux-E Foam may produce reversible HPA axis suppression, Cushing's syndrome, hyperglycemia, and unmask latent diabetes. May increase the risk of cataract and glaucoma.
Diprolene (betamethasone dipropionate) ointment	Corticosteroid (Class I, high potency)	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years and older	Apply twice daily up to 2 weeks; Discontinue when control is achieved	Most common adverse reactions (<1%) are erythema, folliculitis, pruritus, and vesiculation. Can cause reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency during and after withdrawal of treatment. May increase the risk of cataract and glaucoma.
Vanos (fluocinonide) cream	Corticosteroid (Class II, high potency)	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years and older	Apply once or twice daily up to 2 weeks	Most common adverse reactions (≥1%) are headache, application site burning, nasopharyngitis, and nasal congestion. Systemic absorption may produce reversible HPA axis suppression, Cushing's syndrome, hyperglycemia and unmask latent diabetes.
Tazorac (tazarotene) gel	Retinoid	Topical treatment of plaque psoriasis of up to 20% body surface area in patients 12 years and older	Apply once daily	Most common adverse reactions in 10-30% of patients are pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, and skin pain. Tazorac is a teratogen.
Systemic Products				
Enbrel (etanercept) subcutaneous injection	TNF blocker	Plaque psoriasis in patients 4 years and older	Weekly injection	Most common adverse reactions (incidence > 5%): infections and injection site reactions. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Enbrel.
Stelara (ustekinumab) subcutaneous injection	IL-12 and IL-23 antagonist	Moderate to severe plaque psoriasis in patients 6 years and older, who are candidates for phototherapy or systemic therapy	Initial injection, then second dose 4 weeks later, then third dose every 12 weeks	Most common adverse reactions (≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue. Serious infections have occurred; may increase risk of malignancy.

Source: Reviewer's Table from labeling

2.3. Patient Experience Data

Based on the objectives of the trial, the Applicant evaluated only clinician reported outcomes.

	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	X Clinical outcome assessment (COA) data, such as	

		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 7.2.2
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

3. Regulatory Background

In 2013, the FDA approved TOPICORT Topical Spray, 0.25% for the treatment of plaque psoriasis in patients 18 years of age or older. At the time of NDA submission, no trials had been conducted in pediatric subjects. Given this was a new dosage form of desoximetasone, the Pediatric Research Equity Act (PREA) was triggered. The Approval Letter on April 11, 2013 required the Applicant to conduct a deferred study under PREA PMR:

- 2029-1: "Conduct a trial in 100 evaluable pediatric patients with plaque psoriasis ages 2 to 16 years and 11 months. Evaluate the safety and effect of Topicort (desoximetasone) Topical Spray, 0.25% on the hypothalamic-pituitary-adrenal axis and pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment. Conduct the trial in sequential cohorts, for example: 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."
- The Agency waived the pediatric study requirement for ages 0 to 1 year 11 months because of evidence strongly suggesting that the drug product would be unsafe in this pediatric group.

In order to fulfill PMR 2029-1, the Applicant conducted Trial DSXS-1303. On February 6, 2014, the Applicant submitted the protocol for trial DSXS-1303 under IND 101789. On April 18, 2014, the Division of Dermatology and Dentistry (DDD) sent comments to the Applicant regarding the submitted protocol. DDD recommended that a serum cortisol level of ≤ 18 mcg/dL obtained 30 minutes post-cosyntropin stimulation be used to define HPA axis suppression (refer to advice/information request letter dated 4/18/2014 under IND 101789). The Applicant started trial DSXS-1303 on January 23, 2015. However, given enrollment of pediatric subjects with moderate to severe psoriasis involving ≥10% of the body surface area (BSA) was challenging, the Applicant submitted multiple extension requests which were granted by DDD given the Applicant's good faith efforts to complete the trials (letter dates 5/17/2017 and 11/27/2019). On September 5, 2019, the Applicant submitted a partial waiver request that would allow discontinuation of the PK assessment in Cohort 2 (6 to 12 years) and Cohort 3 (2 to 6 years). This request was granted by DDD, and the Applicant was asked to discontinue further enrollment due to safety concerns regarding HPA axis suppression (the level of HPA axis suppression observed in first 2 cohorts was >30%) and analyze the available data.

On April 29, 2020, the Agency received the efficacy supplement with final study report. On June 25, 2020, the Agency issued a refuse to file letter due to deficiencies identified by CMC, clinical pharmacology and clinical reviewers. On December 15, 2020, the Applicant submitted sNDA 204141/S-009 to address these deficiencies, which were adequately addressed. This supplemental NDA (NDA 20414/S-009), included a request for a partial waiver for PK data in pediatric subjects 2-6 years of age (Cohort 3). The Applicant's justification for this waiver request was that enrollment of study subjects had been difficult, and the results in all pediatric age groups studied indicated that HPA axis suppression is greater in children compared to adults treated with TOPICORT Topical Spray, 0.25%.

The Applicant is not seeking an expansion of the labeling for pediatric use. They are reporting that the extent of HPA axis suppression is greater in children aged 2 to less than 18 years of age (36% overall HPA axis suppression in children, versus 14% in adults). Therefore, the Applicant asserts the risk outweighs the potential benefit of use in the pediatric patient population and does not intend to recommend use in pediatric patients. The Applicant is proposing to strengthen the Warning against use in the pediatric population in the labelling in Section 5.1 (Effects on Endocrine System) and describe the results of the study in Section 8.4 (Pediatric Use) of the label for TOPICORT Topical Spray, 0.25%.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. The

Division did not request that the Office of Scientific Investigations (OSI) conduct clinical inspections of sites.

4.2. Product Quality

The Office of Product Quality Reviewer, Joel (Steve) Hathaway, PhD, analyzed the Applicant's request for categorical exclusion from the requirement for an environmental impact analysis statement, per 21 CFR 25.15(d) and 21 CFR 25.31(a). No changes were proposed for the chemistry, manufacturing or controls-related information in the PI or carton-container labeling.

Dr. Hathaway concluded, "CMC evaluation of the supplemental application's labeling and categorical exclusion request found it acceptable … Approval is recommended."

Refer to the review by Joel (Steve) Hathaway, PhD, dated 8/4/2021.

5. Pharmacology and Toxicology

The Applicant submitted no new pharmacology/toxicology data in this pediatric efficacy supplement. The Pharmacology/Toxicology team conducted a comprehensive review of the nonclinical data which was submitted to support the original approval of TOPICORT Topical Spray, 0.25%. For an analysis and discussion of the nonclinical data, refer to the review by Renqin Duan, PhD dated 1/7/2013.

The Pharmacology/Toxicology Reviewer, Renqin Duan, PhD, provided comments regarding the relevant subsections of labeling, Sections 8.1, 8.3, 12.1 and 13.1. Refer to the review by Dr. Duan, dated 8/13/2021.

6. Clinical Pharmacology

See Clinical Pharmacology Review by Soo Hyeon Shin, PharmD, PhD dated 8/18/21.

6.1. Pharmacokinetics

The Applicant conducted a pharmacokinetic (PK) assessment in a total of 25 subjects from Cohorts 1 and 2 by evaluating the percutaneous absorption of desoximetasone following multiple, twice-daily applications of desoximetasone 0.25% topical spray over 28 days. Plasma desoximetasone concentrations were measured from pre-dose blood draws (Cpre) at Visits 2-6 (Days 1, 8, 15, 22, and 29) and full- (Cohort 1) and sparse- (Cohort 2) PK blood sampling at Visit 6 (Day 29).

Mean systemic desoximetasone exposure was higher in the PK subgroups of subjects in Cohorts 1 and 2 exhibiting HPA axis suppression compared to their non-suppressed counterparts, suggesting a systemic mechanism associated with suppression of the HPA axis. Systemic desoximetasone levels were not assessed for the youngest age group, Cohort 3 (2 years to 5 years and 11 months of age). The Applicant is seeking a partial pediatric waiver for the evaluation of PK data in Cohort 3 "based on the impracticable nature of running such a trial within realistic measures and in light of the availability of adrenal suppression results from Cohort 3 with supporting PK data from Cohorts 1 and 2."

The Clinical Pharmacology Reviewer, Soo Hyeon Shin, PharmD, PhD, concluded that, "The observed HPA axis suppression rate in this study was higher than the rate observed in adults (36% vs. 14%). In addition, the high HPA axis suppression rate in Cohort 1 of 35% makes it not possible to carve out a population of pediatric subjects based on age where the treatment benefit could be justified. Therefore, this product should not be recommended for use in pediatric subjects." See Clinical Pharmacology Review by Dr. Shin dated 8/18/21.

The results of the PK assessments will be conveyed to the prescriber in Section 12.3 Pharmacokinetics of the Prescribing Information (PI) for TOPICORT Topical Spray, 0.25%.

6.2. Pharmacodynamics

The results of the HPA axis suppression trial in pediatric subjects will be conveyed to the prescriber in Section 12.2 Pharmacodynamics of the PI for TOPICORT Topical Spray, 0.25%.

7. Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

To address PMR 2029-1, which required the Applicant conduct a deferred study evaluating the safety and effect of TOPICORT Topical Spray, 0.25% on the HPA axis and pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment, the Applicant conducted a single, open-label maximal use Phase 4 (post-marketing) trial (DSXS-1303): *"An Open Label, Safety Study to Assess the Potential for Adrenal Suppression and Pharmacokinetics Following Maximal Use Treatment with TOPICORT (desoximetasone) Topical Spray, 0.25% in Pediatric Patients with Plaque Psoriasis."* The trial is tabulated and summarized below.

Table 2: Clinical Trial DSXS-1303

Trial Identity	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/Follow Up	No. of Subjects	Study Population	No. of Centers and Countries
Studies to Support Safety							
DSXS-1303	Multicenter, open-label, maximal use, HPA axis and safety trial which included PK subgroup analysis	Twice daily for 4 weeks	Primary: HPA axis suppression poten ial; Secondary: PK endpoints, AEs, changes on the PGA score and he Clinical Signs and Symptoms score at the end of treatment	4 weeks treatment dura ion. 3 safety follow up visits (Day 56, Day 84 and Day 112 after discon inuing treatment) for subjects who exhibited signs of adrenal suppression during he study	129	Moderate to severe plaque psoriasis (PGA 3 or 4) with BSA ≥10% and normal HPA axis func ion and adrenal response at Screening; affected age 2-17 years	8 sites in 3 countries (5 in U.S., 2 in El Salvador, 1 in Panama)

Source: Reviewer's Table
Abbreviations: HPA = hypothalamic-pituitary-adrenal; PK = pharmacokinetic; AE = adverse event; PGA = Physician's Global Assessment; BSA= body surface area

7.1.2. Review Strategy

The focus of this review was the local and systemic safety (HPA axis suppression) of TOPICORT Topical Spray, 0.25% and included PK subgroup analysis. The trial's primary objective was not to assess efficacy; however, the Applicant assessed the treatment effect of TOPICORT Topical Spray, 0.25%.

Data Sources
The sources of data used for the evaluation of the efficacy and safety of TOPICORT Topical Spray for the proposed indication included the final study report submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references.

This application was submitted in eCTD format and entirely electronic. The electronic submission including the protocol, clinical study reports, SDTM, and ADaM formats are located in the following network paths:

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\\CDSESUB1\evsprod\NDA204141\0073
\\CDSESUB1\evsprod\NDA204141\0069

Data and Analysis Quality
In general, the data submitted by the Applicant to support the safety of TOPICORT Topical Spray, 0.25% for the proposed indication appears acceptable.

7.2. Review of Relevant Trial

7.2.1. Study Design and Endpoints

Clinical Trial DSXS-1303
Study Population
The key entry criteria that defined the study population are as follows:

Key inclusion criteria:

- Male or female subjects, ages 2 to 17 years, inclusive, at the time of screening.
- Plaque psoriasis involving ≥ 10% total BSA (excluding the face and scalp).
- If a subject has both guttate and plaque psoriasis, the majority of lesions must be plaque type covering a minimum of 5% BSA.
- Clinical diagnosis of moderate or severe plaque psoriasis as defined by a Physician Global Assessment (PGA) score of 3 (moderate) or 4 (severe) at baseline.

- Results from a Cortisol Response Test that are considered normal[12] and show no evidence of any abnormal HPA function or adrenal response at baseline.

Key exclusion criteria:

- Current diagnosis of unstable forms of psoriasis in the treatment area, including guttate, erythrodermic, exfoliative, or pustular psoriasis.
- History of psoriasis that has been unresponsive to topical corticosteroid therapy.
- Use of any topical antipsoriatic agents of any kind or any topical corticosteroids for any reason within 2 weeks prior to first use of study drug.
- Treatment with any systemic steroids within 4 weeks of the first dose of the study drug.
- Treatment with any systemic antipsoriatic therapy or phototherapy (UVB or UVA) within 8 weeks of the first dose of study drug.
- Treatment with any biological therapies for psoriasis within 12 weeks (or five half-lives whichever is less) prior to the first dose of study drug.
- History of allergy or sensitivity to corticosteroids or history of any drug hypersensitivity or intolerance which would compromise the safety of the subject or the results of the study.
- Any serious skin disorder or chronic medical condition that may interfere with the clinical assessments of the signs and symptoms of psoriasis or would place the subject at undue risk by participation in the study
- Female who is pregnant, nursing, planning to become pregnant during the duration of the study, or if of childbearing potential (post-menarchal) and sexually active not willing to use appropriate contraceptive methods.

Study Design

Trial DSXS-1303 was a multicenter, open-label, maximal use, safety trial which included PK subgroup analysis to assess the potential of TOPICORT Topical Spray, 0.25% to suppress HPA axis function in subjects age 2 to less than 18 years with moderate to severe plaque psoriasis involving ≥ 10% BSA (excluding the face and scalp) and normal baseline adrenal function.

After confirmation of eligibility, investigational staff identified treatment sites and instructed subjects (≥ 12 years of age) or caregivers to apply a thin film of the study drug with gentle massage to the affected skin areas with psoriasis twice daily (morning and evening) for 28 days. One hundred twenty nine (129) subjects were enrolled to obtain 100 evaluable subjects[13], and were serially enrolled into 3 cohorts (Cohort 1: 12 years to 17 years and 11 months of age; Cohort 2: 6 years to 11 years and 11 months of age; Cohort 3: 2 years to 5 years and 11 months of age), beginning with Cohort 1. Subsequent cohorts were only initiated if safety criteria

[12] All of the following criteria must have been met for a normal cortisol response test: Basal (pre-CORTROSYN® injection) cortisol concentration > 5 mcg/100 mL, 30 minute post injection cortisol level at least 7 mcg/100 mL greater than the basal level (≥ basal value + 7), and the post stimulation level > 18 mcg/100 mL.
[13] Evaluable subjects are those who had both baseline and end-of-study cortisol response test results, and had not enrolled in the study previously.

regarding HPA axis suppression were met. PK subgroup analysis was performed for Cohort 1 and Cohort 2.

Subjects in non-PK subgroup were evaluated at Screening, Baseline, Week 2 and Week 4 (End of Treatment), as described in Table 5 below. Subjects in PK subgroup were evaluated at Screening, Baseline, Week 1, Week 2, Week 3, Week 4 (End of Treatment), and Day 30, as described in Table 6 below. There were up to 3 planned safety follow-up visits (Day 56, Day 84 and Day 112 after discontinuing treatment) for subjects who exhibited signs of adrenal suppression during the trial or at Day 30 (PK subgroup). At these visits, repeat cortisol response tests were conducted. If the subject had resolved all laboratory abnormalities as early as the first safety follow up visit at Day 56, the subject was discharged from the trial and no additional safety follow up was necessary.

Safety monitoring included adverse event monitoring, laboratory parameters to evaluate HPA axis suppression, and concomitant medication review.[14] Any subject presenting with symptoms of HPA axis suppression (such as nausea, headache, myalgia, fatigue or loose stools) was to be referred to an endocrinologist.

Investigators documented disease severity and body surface area (BSA) at screening and during the treatment period. To assess compliance, study personnel documented the weight of the study product containers and reviewed dosing diaries completed by each subject or caregiver.

Concomitant Medications

Permitted concomitant medications included: inhaled corticosteroids (provided that the subject had been on a stable regimen for at least 2 weeks before the first dose of study drug and would continue during the study), female subjects using hormonal contraceptives (provided that the female subject had been on the same product/dosing regimen for at least 28 days before and did not change this during the study), and anti-histamines (provided that the subject had been on a stable dose for at least 2 weeks before enrollment and would remain on a stable dose throughout the trial). Prohibited products with associated washout periods are listed below in Table 3.

Table 3: Prohibited Products

[14] HPA axis suppression was defined as 30- minute post-CORTROSYN injection serum cortisol level of ≤ 18 mcg/100 mL, at Day 30 Post Treatment

Product	Washout period prior to first application of study product
New regimens of inhaled corticosteroids	2 weeks
New regimens of anti-histamines	2 weeks
Any topical antipsoriatic agents of any kind	2 weeks
Any topical corticosteroids for any reason	2 weeks
Any systemic steroids (with the exception of contraceptives)	4 weeks
Any immunosuppressant medication	4 weeks
Any systemic antipsoriatic therapy or phototherapy (UVB or UVA)	8 weeks
Any biological therapies for psoriasis	12 weeks (or five half-lives, whichever is less)
High strength (20% or above) alpha-hydroxy acid or any kind of peel on the treatment area	Not specified
Any other treatments, prescription or OTC products for the treatment of any other dermatological condition including: antibacterial, medicated and/or astringent washes, soaps, pads or moisturizers	Not specified

Source: Reviewer's Table

Objectives and Related Endpoints

The primary objective of the trial was to evaluate the potential of TOPICORT Topical Spray, 0.25% to suppress HPA axis function in pediatric subjects age 2-17 years with moderate to severe plaque psoriasis involving ≥ 10% BSA. The secondary objectives were to evaluate efficacy parameters, PK and AE profile.

The primary outcome endpoint was HPA axis response to cosyntropin demonstrating the absence or presence of adrenal suppression at the end of the treatment. The secondary outcome endpoints were: changes on the PGA score at the end of treatment, changes on the Clinical Signs and Symptoms scores (erythema, scaling, plaque elevation) at the end of treatment, and PK parameters for desoximetasone at the end of treatment.

Investigators

A total of 8 study sites enrolled subjects for this trial and were located in the United States (5), El Salvador (2), and Panama (1). Two study sites in the United States did not enroll subjects.

Table 4: Study Sites and Enrollment

Site Number	Principal Investigator	Location	Subjects Enrolled (N)
1	Lorely E. Mendez, MD	Miami, FL, USA	12
2	Joe Blumenau, MD	Dallas, TX, USA	0
3	Melody Lynn Stone, MD	St. Joseph, MO, USA	3
4	Marta B. Quesada Ramirez, MD	Panama City, Panama	27
5	Altagracia A. Victoria, MD	Hialeah, FL, USA	4
6	Maria Carballosa, MD	Hialeah, FL, USA	54
7	Ana M. Elosegui, MD	Sweetwater, FL, USA	3
8	Bruce Torkan, MD	Los Angeles, CA, USA	0
9	Rolando E. Julian Gonzalez, MD	San Salvador, El Salvador	13
10	David E. Zepeda Reyes, MD	Santa Tecla, El Salvador	13

Source: Reviewer's Table from Clinical Study Report Table 6.1

Table 5: Schedule of Assessments, Non-PK subgroup subjects

PROCEDURE	VISIT 1 Day -14 to -1 Before 12 pm	VISIT 2 Day 1	VISIT 3 Day 15 ± 2 days	VISIT 4 Day 29 ± 2 days Before 12 pm
	Screening	Baseline	Interim Visit	End of Treatment/ ET
Informed Consent	X			
Medical History & Demographics	X			
Physical Exam	X			X
Confirm Inclusion/Exclusion Criteria	X	X		
Vital Signs	X	X		X
Dermatological Assessment (Clinical Signs and Symptoms/PGA Score)	X	X	X	X
% BSA Assessment	X	X	X	X
Pregnancy Test	X	X		X
Concomitant Medication	X	X	X	X
Cortisol Response Test	X			X
Dispense Sunscreen and Wristband		X		
Weigh & Dispense Study drug		X	X	
Complete AM dose at the clinic		X		
Collect & Weigh Study drug			X	X
Dispense/Review patient Dosing Diary		X	X	X
Adverse Events			X	X
Diary Collection and Evaluation of Protocol Compliance			X	X

Source: Clinical Study Report, page 29

Table 6: Schedule of Assessments, PK subgroup subjects

PROCEDURE	VISIT 1 Day -14 to -1 Before 12 pm	VISIT 2 Day 1	VISIT 3 Day 8 ± 2 days	VISIT 4 Day 15 ± 2 days	VISIT 5 Day 22 ± 2 days	VISIT 6 Day 29 ± 2 days	VISIT 7 Day 30 + 1 day Before 12 pm
	Screening	Baseline	Interim Visit	Interim Visit	Interim Visit	End of Treatment/ET	Post-Treatment
Informed Consent	X						
Medical History & Demographics	X						
Physical Exam	X					X	
Confirm Inclusion/Exclusion Criteria	X	X					

Vital Signs	X	X				X	X
Dermatological Assessment	X	X	X	X	X	X	
% BSA Assessment	X	X	X	X	X	X	X
Pregnancy Test	X	X				X	
Concomitant Medication	X	X	X	X	X	X	X
Collect Plasma Drug Level (morning pre-dose) Sample		X	X	X	X	X	
Pharmacokinetic Profile (post-dose) Sampling						X	
Cortisol Response Test	X					X	X
Dispense Sunscreen and Wristband		X					
Complete AM dose at the clinic		X				X	
Weigh & Dispense Study drug		X		X			
Collect & Weigh Study drug				X		X	
Dispense/Review Subject Dosing Diary		X	X	X	X	X	X
Adverse Events			X	X	X	X	X
Evaluation of Protocol Compliance			X	X	X	X	X

Source: Clinical Study Report, page 30

Data Analysis

Subjects who used the study product were included in the Safety Population. Subjects were considered 'evaluable' for HPA axis function analyses if they completed the study and had both baseline and end-of study (Week 4) cortisol results. Subgroups of subjects in Cohorts 1 and 2 were included in PK evaluations if at least one post-dosing PK sample (Day 8 and onwards) was collected and assayed.

Since the trial was an open-label trial and was not powered sufficiently to perform efficacy statistical analysis, the Applicant reports descriptive analyses on the mean change from baseline to end of treatment in PGA scores and Clinical Signs and Symptoms scores (erythema, scaling, plaque elevation).

Protocol Amendments

There were 6 versions of the Protocol DSXS-1303. The Applicant submitted all versions to the Division for review. Key amendments to the final versions of the protocol included: updating the inclusion criteria to include a minimum PGA score of 3 (moderate) and a maximum PGA score of 4 (severe); clarifying the percent of affected BSA required for entry into the trial (≥10% of the body); removing the maximal total BSA to be treated; adding a Screening visit for PK and

non-PK sampling groups; assuring that Cohorts 2 and 3 would not be initiated until Cohort 1 results had been analyzed; specifying cohort stopping criteria [if during the study more than 35% of dosed subjects from each cohort were considered to be exhibiting signs, confirmed by the results of a cortisol response test, and/or symptoms (nausea, headache, fatigue, myalgia or loose stool) of HPA axis suppression, the enrollment for this cohort would be stopped and the enrollment for a younger cohort would not be initiated]; defining potential HPA axis suppression; removing a 6-month enrollment limit to allow for longer recruitment periods; documenting the procedure for patients who exhibited abnormal cortisol response test results and specifying criteria for referral to an endocrinologist.

7.2.2. Results of Efficacy Assessment

Evaluation of treatment effect: Since this open-label trial was not powered sufficiently to perform efficacy statistical analysis, the Applicant reports descriptive analyses on the mean change from baseline to end of treatment in PGA scores and Clinical Signs and Symptoms scores (erythema, scaling, plaque elevation). Therefore, evaluation of treatment effect was assessed.

Physician Global Assessment (PGA) Score
At all visits a visual inspection to confirm a diagnosis of chronic plaque psoriasis was done. PGA scores (also referred to as the Investigator's Global Assessment scores) were assessed at each visit on a 5-point scale, outlined in Table 7 below.

Clinical Signs and Symptoms of Psoriasis
Clinical signs and symptoms of chronic plaque psoriasis (erythema, scaling, plaque elevation) were assessed at each visit on a 5-point scale: 0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe, 5=very severe.

Affected Percent Body Surface Area Assessment (%BSA)
The %BSA affected with plaque psoriasis (excluding face and scalp) was assessed during each clinic visit by the investigator using the "Rule of Nines" method of approximation.

Table 7: Investigator's Global Assessment Scale

Score	Category	Description
0	Clear	No psoriatic lesions, i.e., no plaque formation; no erythema, no induration, no scaling.
1	Almost Clear	No more than minimal scaling or minimal residual erythema. No more than minimal plaque elevation just above normal skin level.
2	Mild	Scaling present although not extensive. Plaque elevation, discernible 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: Reviewer's table adapted from Protocol Version 6, Appendix B

The study's primary endpoint was HPA axis suppression potential and secondary endpoints were changes in PGA score and Clinical Signs and Symptoms of psoriasis scores, and PK parameters. Subjects who used at least 42 doses of the study drug and had at least one post-baseline dermatological examination performed were included in the efficacy evaluations.

(b) (4)

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Table 8: Summary of PGA Scores by Visit

Visit	Statistic	Cohort 1 (N=84)	Cohort 2 (N=35)	Cohort 3 (N=10)
Day 1	Mean PGA Score ± SD	(b) (4)		
	n			
Day 29	Mean PGA Score ± SD			
	n			

Source: Reviewer's Table adapted from Clinical Study Report Table 11.3.1.5
Abbreviations: PGA = Physician Global Assessment; SD = Standard Deviation

Table 9: Summary of Clinical Signs and Symptoms Scores by Visit

Sign and Symptom	Visit	Statistic	Cohort 1 (N=84)	Cohort 2 (N=35)	Cohort 3 (N=10)
Erythema	Day 1	Mean Score ± SD n	(b) (4)		
	Day 29	Mean Score ± SD n			
Plaque	Day 1	Mean Score ± SD n			
	Day 29	Mean Score ± SD n			
Scaling	Day 1	Mean Score ± SD n			
	Day 29	Mean Score ± SD n			

Source: Reviewer's Table adapted from Clinical Study Report Table 11.3.1.6
Abbreviations: SD = Standard Deviation

Table 10: Summary of %BSA Assessments

Visit	Statistic	Cohort 1 (N=84)	Cohort 2 (N=35)	Cohort 3 (N=10)
Day 1	Mean %BSA ± SD n	(b) (4)		
Day 29	Mean %BSA ± SD n			

Source: Reviewer's Table adapted from Clinical Study Report Table 14.1.5
Abbreviations: BSA = Body Surface Area; SD = Standard Deviation

7.3. Review of Safety

7.3.1. Safety Review Approach

The review of the safety of TOPICORT Topical Spray, 0.25% in the pediatric population age 2 to less than 18 years of age focused on data from a single trial, DSXS-1303. The analyses included treatment emergent adverse events (TEAEs), serious AEs (SAEs), AEs leading to discontinuation, adverse reactions (ARs) and AEs associated with the product class, corticosteroids.

7.3.2. Review of Safety Database

Exposure

Extent of Exposure

Subjects were instructed to apply a thin, uniform layer of the test article to the designated treatment area twice a day for 28 days. In the 129 enrolled subjects, the mean duration of exposure was 26 days, the mean total number of doses applied was 50, and the mean total number of missed doses was 6.

For safety analyses, all subjects who applied at least one dose of study drug were included. For efficacy analyses, subjects who used at least 42 doses of the study drug and had at least one post-baseline dermatological examination performed were included.

Summaries of the mean amounts of study product used in the evaluable and PK subgroup populations are shown in Table 11 and are generally comparable considering the variability of the cohorts.

Table 11: Summary of Mean Amounts of Study Product Used

	Cohort 1	Cohort 2	Cohort 3
Evaluable Population (N = 100)			
Number of subjects (n)	60	30	10
Mean Amount (g) ± SD	95.5 ± 38.5	77.2 ± 40.7	85.5 ± 27.2
PK Subgroup (N = 25)			
Number of subjects (n)	16	8	0
Mean Amount (g) ± SD	76.1 ± 45.3	97.4 ± 54.5	—

Source: Reviewer's Table adapted from Integrated Summary of Safety Table 11
Abbreviations: SD = Standard Deviation
Note: Amount used defined as bottle weight 1 (dispensed-collected) + bottle weight 2 (dispensed-collected)

Characteristics of the Safety Population

Demographic and Baseline Characteristics

Summaries of the demographic data are shown in Tables 12 and 13 below. Most of the subjects were white Hispanic or Latino. Given the small sample sizes, the overall baseline demographics were relatively balanced between cohorts in terms of sex and ethnicity. Given the age differences across cohorts, associated demographic characteristics of age, weight and height expectedly differed across cohorts. Baseline disease severity (in terms of mean PGA score, Clinical Signs and Symptoms scores and %BSA affected) was relatively comparable across cohorts. The mean screening PGA scores were 3.3, 3.1, and 3 for Cohort 1, Cohort 2, and Cohort 3 respectively; the mean screening erythema scores were 3.2, 3.1, and 3 for Cohort 1, Cohort 2, and Cohort 3 respectively; the mean screening plaque scores were 3.3, 3.1, and 2.7 for Cohort 1, Cohort 2, and Cohort 3 respectively; the mean screening scaling scores were 3.3, 3.2, and 2.8 for Cohort 1, Cohort 2, and Cohort 3 respectively; and the mean screening %BSA values were 16.2, 18.8, an 16.3 for Cohort 1, Cohort 2, and Cohort 3 respectively.

Table 12: Summary of Demographic Data (Safety Population)

Characteristic	Statistic	Cohort 1	Cohort 2	Cohort 3
Age (years)	n	84	35	10
	Mean	14.2	9.2	3.4
	Median	14	9	3
	Range	12 - 17	7 - 11	2 - 5
Sex	Male	35 (41.7%)	23 (65.7%)	4 (40.0%)
	Female	49 (58.3%)	12 (34.3%)	6 (60.0%)
Ethnicity	Hispanic or Latino	81 (96.4%)	35 (100.0%)	10 (100.0%)
	Not Hispanic or Latino	3 (3.6%)	0 (0.0%)	0 (0.0%)
Race	American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Black or African American	1 (1.2%)	0 (0.0%)	0 (0.0%)
	White	70 (83.3%)	22 (62.9%)	10 (100.0%)
	Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	13 (15.5%)	13 (37.1%)	0 (0.0%)
	Multiple	0 (0.0%)	0 (0.0%)	0 (0.0%)
Weight (kg)	Mean	59.8	37.8	17
	Median	57.5	39.5	16
	Range	30 - 112.5	22.5 - 61	13 - 29.5
Height (cm)	Mean	162	135.4	102.7
	Median	159	135	99
	Range	130 - 439	121 - 153	88 - 125
Screening PGA Score	Mean	3.3	3.1	3
	Median	3	3	3
	Range	3 - 4	3 - 4	3 - 3
Screening Erythema Score	Mean	3.2	3.1	3
	Median	3	3	3
	Range	1 - 5	3 - 4	3 - 3
Screening Plaque Score	Mean	3.3	3.1	2.7
	Median	3	3	3
	Range	2 - 4	3 - 4	2 - 3
Screening Scaling Score	Mean	3.3	3.2	2.8
	Median	3	3	3
	Range	3 - 5	3 - 4	2 - 3
Screening %BSA	Mean	16.2	18.8	16.3
	Median	12	16	15
	Range	10 - 50	11 - 38	12 - 32

Source: Reviewer's Table adapted from Clinical Study Report Tables 14.1.1, 14.1.3, 14.1.4, 14.1.5

Table 13: Summary of Demographic Data (Safety Population) – PK Subgroup

Characteristic	Statistic	PK Subgroup Cohort 1	PK Subgroup Cohort 2
Age (years)	n	17	8
	Mean	14.9	9.3
	Median	15	9
	Range	12 - 17	7 - 11
Sex	Male	3 (17.6%)	5 (62.5%)
	Female	14 (82.4%)	3 (37.5%)
Ethnicity	Hispanic or Latino	17 (100.0%)	8 (100.0%)
	Not Hispanic or Latino	0 (0.0%)	0 (0.0%)
Race	American Indian or Alaska Native	0 (0.0%)	0 (0.0%)
	Asian	0 (0.0%)	0 (0.0%)
	Black or African American	0 (0.0%)	0 (0.0%)
	White	12 (70.6%)	8 (100.0%)
	Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)
	Other	5 (29.4%)	0 (0.0%)
	Multiple	0 (0.0%)	0 (0.0%)
Weight (kg)	Mean	54.3	34.9
	Median	54	33.8
	Range	33 - 83.5	23 - 46.5
Height (cm)	Mean	159.1	134.4
	Median	159	135
	Range	142 - 177	126 - 153

Source: Reviewer's Table adapted from Clinical Study Report Table 14.1.2

Concomitant Medications

A total of 23 (18%) subjects used 14 concomitant medications during the trial. The most common class of medications were “topical emollients.” In this class, the most frequently reported products were sunscreen (14/129, 11%), and sunblock (2/129, 1.5%). Other concomitant medications included ibuprofen, fluticasone, montelukast, albuterol, famotidine, topical vitamin D analogs (2/129, 1.5%), topical tacrolimus (2/129, 1.5%), ethinyl estradiol levonogestrel, methylphenidate, mineral oil, oral vitamin D, and Dermaglos. The topical vitamin D analogs and topical tacrolimus medications for treatment of psoriasis were started after the 4 week treatment period, during the study follow-up period, and therefore should not have affected the efficacy assessments.

Disposition

A total of 129 subjects enrolled, and 106 subjects completed the study. Twenty-three subjects terminated early for reasons including abnormal lab results, a laboratory error in the cortisol response test procedures, and previous enrollment in the study at another site. There were no discontinuations due to adverse events. A summary of subject disposition is shown in Table 14 below.

Table 14: Summary of Subject Disposition

Disposition	Cohort 1	Cohort 2	Cohort 3	Total	Cohort 1 PK Subgroup	Cohort 2 PK Subgroup	Total
Enrolled	84	35	10	129	17	8	25
Completed Study[1]	66	30	10	106	11	8	19
Evaluable[2]	60	30	10	100	11	8	19
Terminated Early	18	5	0	23	6	0	6

Source: Reviewer's Table adapted from Clinical Study Report Tables 10.1.1, 10.1.2

[1] Completed subjects are those who completed their final visit

[2] Evaluable subjects are those who had both baseline and end-of-study Cortisol Response Test results, and had not enrolled in the study previously

Protocol Deviations

Of the 129 enrolled subjects, 38 subjects had 57 protocol deviations. A summary of protocol deviations is shown below in Table 15. The majority of protocol deviations (46/57, 81%) are classified by the Applicant as "Other." Of the subjects who had a protocol deviation of "Other," 16 subjects did not complete their follow up Cortisol Response Test despite their last test being abnormal, 7 subjects were re-dispensed the first bottle of investigational product rather than getting a new bottle as insufficient investigational product was available on site at the time, and 1 subject with signs of HPA axis suppression was not referred to an endocrinologist.

Table 15: Summary of Protocol Deviations

Characteristic	Cohort 1 (n=84)	Cohort 2 (n=35)	Cohort 3 (n=10)	Total (n=129)
Total Subjects with Protocol Deviations	27	11	0	38
Total Deviations	43	14	0	57
Outside Visit Window	7	3	0	10
Missed Visit	1	0	0	1
Other	35	11	0	46

Source: Reviewer's Table adapted from Clinical Study Report Table 10.2.1

Adequacy of the Safety Database

The demographics of the study population are sufficiently representative of the target population. The safety database presented by the Applicant is adequate.

Mean systemic desoximetasone exposure was higher in the PK subgroups of subjects in Cohorts 1 and 2 exhibiting HPA axis suppression compared to their non-suppressed counterparts, suggesting a systemic mechanism associated with suppression of the HPA axis. Systemic desoximetasone levels were not assessed for the youngest age group, Cohort 3 (2 years to 5 years and 11 months of age). The Applicant is seeking a partial pediatric waiver for the evaluation of PK data in Cohort 3 "based on the impracticable nature of running such a trial within realistic measures and in light of the availability of adrenal suppression results from Cohort 3 with supporting PK data from Cohorts 1 and 2." The Applicant requests the Agency accept extrapolation of systemic exposure data from Cohorts 1 and 2 pediatric populations to the youngest age cohort, and states "Extrapolation of the exposure data (PK) from Cohorts 1 and 2 to Cohort 3 is appropriate based on similar disease pathogenesis, disease course, and criteria for disease definition in adults and pediatrics ... The likelihood of attaining targeted

enrollment for the Cohort 3 PK subgroup could stretch the trial duration up to a decade. This is not only due to the low prevalence of plaque psoriasis in such a pediatric age group but also parental concerns of exposing children to phlebotomy required for study evaluations in the PK component of the study."

The Pediatric Review Committee (PeRC) convened on 7/13/21 and agreed with the Division's recommendation that the indication for TOPICORT Topical Spray, 0.25% should not be expanded to the pediatric population, agreed with the proposed updates to the labeling to include an update to the warning section as well as Section 8.4 to recommend not using in pediatrics, and agreed PMR 2029-1 should be considered fulfilled.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
The overall the quality of the data submitted is adequate to characterize the safety of TOPICORT Topical Spray, 0.25% applied twice daily for 4 weeks in subjects aged 2 to less than 18 years of age. No significant deficiencies were discovered that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events
The Applicant defined an adverse event (AE) as "any untoward medical occurrence in a patient or clinical-trial patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment." This includes any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs were categorized by body system or organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The Applicant coded adverse events (AEs) using MedDRA, version 21.1.

Investigators graded AEs by seriousness, severity/intensity (mild, moderate, or severe), causality, and action taken with the study product. Serious Adverse Events (SAEs) were defined as AEs or Suspected Adverse Reactions which resulted in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect, any "other" important medical event.

Routine Clinical Tests
AEs and concomitant medications were recorded at each visit. Dermatological assessments (Clinical Signs and Symptoms and PGA scores) and %BSA assessments were performed at each visit. A physical examination was performed and vital signs were assessed at the first and last visits. Laboratory testing was performed per the schedule of assessments (Table 4 and Table 5), and included: cortisol response tests, plasma drug level collections for the PK subgroups, and pregnancy testing.

7.3.4. Safety Results

Deaths, Serious Adverse Events (SAEs), and Discontinuations Due to Adverse Events (AEs)
There were no deaths, SAEs, or discontinuations due to AEs.

Adverse Events
One subject (1/129, 0.8%) reported an AE of headache (Subject (b) (6)). The subject was a 15-year-old, white, non-Hispanic, non-Latino female, with a medical history of plaque psoriasis and acid reflux. On (b) (6) (Study Day 15), the subject experienced a headache which was graded mild in severity (defined as "an AE that is easily tolerated") and was treated with a single dose of ibuprofen 400 mg po. The headache resolved on the same day. There was no change in study drug administration. The Investigator considered the event to be possibly related to the study drug.

This subject also developed biochemical alterations suggestive of potential HPA axis suppression during the study: pre-treatment results showed a basal cortisol level of 9 µg/100 mL and a 30-minute post-injection level of 22 µg/100 mL; after approximately 28 days of treatment, the subject's basal cortisol level was at a normal range of 7 µg/100mL and the 30-minute post-injection level was 17 µg/100 mL, below the threshold value. The subject did not return to the site for the scheduled safety follow-up visit and was not referred to an endocrinologist (with both events documented as protocol deviations).

Other than this single headache event, the Applicant reports that none of the remaining subjects in any cohort experienced HPA axis suppression symptoms of nausea, headache, myalgia, fatigue, or loose stool. No application site reactions are reported.

See Section 7.3.5 below for a summary of HPA axis suppression rates seen in the study.

Adverse Reactions
The Investigator was to determine whether or not there was a reasonable causal relationship between the study drug and the AE, categorized as either "not related: this applies to any AE that is clearly not related to use of the study drug, possible: this means the association of the AE with the study drug is unknown; however, a relationship between drug and event cannot be ruled out, probable: there is a reasonable temporal relationship between the use of the study drug and the AE; based upon the Principal Investigator's clinical experience, the association of the event with the study drug seems likely, [or] definite: the AE occurs following the application of the study drug and it cannot be reasonably explained by any known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient."

The Investigator considered the single AE of headache (Subject (b) (6)) described above in Adverse Events to be possibly related to the study drug.

Since no new local or systemic safety signal was identified, no new addition to labeling Section 6.1 will be made.

Laboratory Findings
See Section 7.3.5. Analysis of Submission-Specific Safety Issues for the discussion of the laboratory findings related to HPA axis suppression.

Vital Signs
Examination of shift tables of vital signs demonstrated no clinically meaningful changes from Baseline and no adverse events related to vital sign abnormalities.

Electrocardiograms (ECGs) and QT
The Applicant did not conduct ECG monitoring during this Trial DSXS-1303. In the original application, the Division granted the request for a waiver to submit data from a thorough QT/QTc study based on low systemic exposure and lack of a cardiac safety signal for the moiety.

Immunogenicity
As the product is not a therapeutic protein, the Applicant did not assess the potential for immunogenicity.

7.3.5. Analysis of Submission-Specific Safety Issues

HPA Axis Suppression
The clinical development program for TOPICORT Topical Spray, 0.25% consisted of a Phase 1, open-label trial (Trial DSXS-0805), assessing the potential for TOPICORT Topical Spray, 0.25% to suppress HPA axis function in 24 adult subjects with moderate to severe plaque psoriasis. Out of the 21 subjects who had evaluable serum cortisol levels, HPA axis suppression, defined as serum cortisol level ≤18 mcg/dL 30-minutes post-cosyntropin stimulation test, was observed in 14% (3/21) of subjects.

In the pediatric Trial DSXS-1303 submitted with this sNDA, HPA axis suppression (defined in the same way as the adult trial, as serum cortisol level ≤18 μg/100 mL 30 minutes post-cosyntropin stimulation at the end of treatment after 28 days of TOPICORT Topical Spray, 0.25% twice daily application) was identified in 36% (36/100) of evaluable subjects. HPA axis suppression rates were 35% (21/60) in Cohort 1, 43.3% (13/30) in Cohort 2, and 20% (2/10) in Cohort 3. These findings are summarized in Table 16 below. Other than the single subject with a headache described in Section 7.3.4 Safety Results above, none of the remaining subjects in any cohort experienced other symptoms consistent with HPA axis suppression such as nausea, myalgia, fatigue, or loose stools. Subjects who exhibited signs of HPA axis suppression at the end of treatment were to follow up at 28 days after treatment cessation, for up to 3 safety follow up visits at Day 56, Day 84, and Day 112. At these visits, repeat cortisol response tests were conducted. If the subject had resolved all laboratory abnormalities as early as the first safety follow-up visit at Day 56, the subject was discharged from the trial and no additional safety follow up was necessary. Of the 36 subjects with HPA axis suppression, HPA axis suppression

ultimately resolved in 29 subjects (80.6%) after treatment cessation. However, the other 7 subjects were lost to follow up or refused follow up testing, therefore the true incidence of HPA axis suppression resolution in this trial is unclear.

Mean systemic desoximetasone exposure was higher in the PK subgroups of subjects in Cohorts 1 and 2 exhibiting HPA axis suppression compared to their non-suppressed counterparts, suggesting a systemic mechanism associated with suppression of the HPA axis. Systemic desoximetasone levels were not assessed for the youngest age group, Cohort 3. For Cohort 1, mean pre-dose concentration at steady-state ($C_{pre\text{-}ss}$) and mean peak plasma concentration at steady-state ($C_{max\text{-}ss}$) on Day 29 were 2.1- and 2.8-fold higher, respectively, for adrenally suppressed subjects compared to non-suppressed subjects. For Cohort 2 , $C_{pre\text{-}ss}$ and $C_{max\text{-}ss}$ on Day 29 were 1.7- and 2.2-fold higher, respectively, for adrenally suppressed subjects compared to non-suppressed subjects. These findings are summarized in Table 17 below.

Ali Mohamadi, MD, Medical Reviewer, Division of Metabolism and Endocrinology Products (DMEP), stated: "There is no set precedent in previous pediatric studies that defines a concerning percentage of patients demonstrating HPA axis suppression ... nonetheless [when considering a comparison to the adult trial data] a cutoff in the 20-30% range seems reasonable" (See review dated 12/5/2012).

Shivangi Vachhani, MD, Medical Reviewer, Division of General Endocrinology (DGE), concluded: "Given the Applicant's definition of HPA axis suppression during the pediatric trial was not consistent with standard practice, this study may have over-estimated the rate of HPA axis suppression see in children. In study DSXS-1303, HPA axis suppression was defined as cortisol ≤ 18 mcg/dL 30 minutes post-cosyntropin stimulation. However, in standard practice, a cortisol level of ≥ 18 mcg/dL at either 30-minutes or 60-minutes post cosyntropin administration is considered a normal response ... Of note, the phase 1 trial evaluating the HPA axis in adults used the same definition for HPA axis suppression as the pediatric trial (serum cortisol level ≤ 18 mcg/dL 30-minutes post cosyntropin stimulation test), so a direct comparison of the risk of HPA axis suppression between children and adults based on these data is reasonable, and it may be concluded that pediatric patients have a greater risk for HPA axis suppression compared to adult patients after treatment with Topicort ... In conclusion, DGE agrees that Topicort Topical spray, 0.25% should not be recommended for use in any age pediatric patients, and DGE agrees with the Applicant's proposed labeling changes. DGE also agrees that it is reasonable to allow a waiver for studying additional pediatric patients in order to fulfill the pediatric PMR" (See review dated 3/24/21).

The Clinical Pharmacology team, acknowledging Dr. Vachhani's consultation, concluded: "The Applicant defined HPA axis suppression as a cortisol level of ≤18 μg/dL 30 minutes poststimulation which is used by the Agency. A consultation review from Dr. Shivangi Vachhani, Clinical Reviewer, Division of General Endocrinology (DGE), stated that the criteria for HPA axis suppression commonly used in clinical practice is <18 μg/dL and not ≤18 μg/dL. According to Dr. Vachhani, if the cutoff criteria of <18 μg/dL is used, then a total of 31 (31%) subjects,

including 19 (32%) subjects in Cohort 1, 10 (33%) subjects in Cohort 2 and 2 (20%) subjects in Cohort 3, would have been classified as having HPA axis suppression.

It is noted that using either criteria for HPA axis suppression, the rate of HPA axis suppression observed in this study is considered as high, and thus the overall conclusion that this product should not be recommended in pediatrics would remain the same." (See Clinical Pharmacology Review by Soo Hyeon Shin, PharmD, PhD dated 8/18/21).

Table 16: Summary of HPA Axis Suppression

Characteristic	Cohort 1	Cohort 2	Cohort 3
Total Evaluable Subjects[1]	60	30	10
Subjects with HPA Axis Suppression[2]	21 (35%)	13 (43.3%)	2 (20%)
Subjects with at least one safety follow-up visit	18	13	2
Subjects with resolved HPA axis suppression after treatment cessation	16	11	2
Subjects with continued HPA axis suppression after treatment cessation	2	2	0

Source: Reviewer's Table adapted from Clinical Study Report and Integrated Summary of Safety Table 31

[1] Evaluable subjects are those who had both baseline and end-of-study cortisol response test results, and had not enrolled in the study previously

[2] HPA axis suppression is defined as serum cortisol level ≤18 µg/100 mL 30 minutes post-cosyntropin stimulation at the end of treatment

Table 17: Summary of PK Parameter Values for PK Subgroups

Statistic	Cohort 1 PK Subgroup		Cohort 2 PK Subgroup	
	Suppressed	Non-Suppressed	Suppressed	Non-Suppressed
Number of subjects	5	11	4	4
$C_{pre\text{-}ss}$ (pg/mL) Mean (range)	2440.8 (1475.00 – 3743.00)	1181.71 (0.00 – 7303.70)	1112.98 (150.80 – 1751.60)	649.53 (81.00 – 2116.50)
$C_{max\text{-}ss}$ (pg/mL) Mean (range)	3544.63 (2346.40 – 4544.50)	1257.64 (51.10 – 7303.70)	1538.65 (150.80 – 2386.30)	694.08 (94.20 – 2116.50)

Source: Reviewer's Table adapted from Integrated Summary of Safety Table 14

7.3.6. Safety Analyses by Demographic Subgroups

In view of the small sample size and the single AE, the analysis of TEAE by demographic subgroup has limited utility.

7.3.7. Supportive Safety Data From Other Clinical Trials

The Applicant conducted a comprehensive search of the worldwide literature on July 8, 2020 to identify sources of pediatric clinical safety information for desoximetasone. Four randomized comparative clinical trials that included adults as well as subjects younger than 18 years treated with desoximetasone were identified. Safety findings included: for subjects treated with BID desoximetasone cream, 0.25% transient, slight burning initially and folliculitis after 13 days of treatment were reported in 1 subject each; age of subjects was not reported, and causal relationship was uncertain.

7.3.8. Safety in the Postmarket Setting

Postmarket safety experience based on data obtained from FDA's FAERS Public Dashboard, and Taro's pharmacovigilance database, includes one case of a 3-year-old with nasal discomfort after accidental exposure to desoximetasone topical spray, 3% after nasal administration. One case (b) (6)) of a 14-year-old patient treated with desoximetasone ointment, 0.25%, includes terms consistent with HPA axis suppression, although exposure data is not available.

Expectations on Safety in the Postmarket Setting
The analysis of the TOPICORT Topical Spray, 0.25% safety data identified no additional significant safety signals in the pediatric population.

Updated language for Ophthalmic Adverse Reactions from new class labeling changes for topical corticosteroids will be added to Section 6.2 Postmarketing Experience of labeling (and also to Section 5 Warnings and Precautions).

7.4. Summary and Conclusions

7.4.1. Statistical Issues

Since this open-label trial was not powered sufficiently to perform efficacy statistical analysis, the Applicant reports descriptive analyses on the mean change from baseline to end of treatment in PGA scores and Clinical Signs and Symptoms scores (erythema, scaling, plaque elevation). Agency statistical review was not performed for this sNDA efficacy supplement.

7.4.2. Conclusions and Recommendations

To evaluate the safety and effect of TOPICORT Topical Spray, 0.25% on the HPA axis and pharmacokinetics of desoximetasone under maximal use conditions after 4 weeks of treatment, the Applicant conducted Trial DSXS-1303. This was an open-label trial which included PK subgroup analysis and enrolled 129 subjects 2 to less than 18 years of age with moderate to severe plaque psoriasis who were treated under maximal use conditions. Although the trial did not primarily evaluate efficacy, (b) (4)

The Applicant assessed the safety of TOPICORT Topical Spray, 0.25% in the target pediatric population. The size of the safety database and the safety evaluations were sufficient to identify local and systemic treatment-emergent adverse reactions. The submitted safety and PK data indicate that use of TOPICORT Topical Spray is not appropriate in the pediatric population given the extent of HPA axis suppression in children 2 to less than 18 years of age is greater than in the adult population (36% in the pediatric population and 14% in the adult population). Therefore, TOPICORT Topical Spray, 0.25% should not be expanded for use in the pediatric population and should remain marketed for the topical treatment of plaque psoriasis in patients 18 years of age or older.

8. Advisory Committee Meeting and Other External Consultations

8.1. The Agency conducted no Advisory Committee Meeting regarding this application because the

The Agency conducted no Advisory Committee Meeting regarding this application because the safety profile of the moiety is well characterized.

9. Pediatrics

In Trial DSXS-1303, the Applicant evaluated the pharmacokinetics and safety of TOPICORT Topical Spray, 0.25% in the target pediatric population with moderate to severe plaque psoriasis. The Pediatric Review Committee (PeRC) agreed with the Division that this assessment was sufficient to fulfil PMR 2029-1 (PeRC Meeting, 7/13/21). The DPMH Pediatrics Reviewer, Shamir Tuchman, MD, supported the decision to maintain the indication for patients 18 years of age or older, and not expand the indication to the pediatric population, given safety findings of HPA axis suppression in the pediatric population.

A description of the trial and results will be included in Section 8.4 Pediatric Use and Section 12 Clinical Pharmacology of labeling to convey to the prescriber the HPA axis suppression potential of TOPICORT Topical Spray, 0.25% in pediatric patients younger than 18 years.

At this time, no additional postmarketing requirements or commitments for deferred pediatric studies are needed under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)).

10. Labeling Recommendations

10.1. Prescribing Information

The Applicant submitted proposed Prescribing Information (PI) for TOPICORT Topical Spray, initially in the Physician Labeling Rule (PLR) format and then later in the Pregnancy and Lactation Labeling Rule (PLLR) format. Shamir Tuchman, MD from the Division of Pediatric and Maternal Health (DPMH), reviewed the proposed labeling and proved recommendations regarding the pediatric population in accordance with 21 CFR 201.57(c)(9)(iv). Clinical comments regarding the content of labeling are integrated into the relevant sections of this review.

The members of the primary review team who provided recommendations regarding PI are

tabulated below. Refer to the reviews by Dr. Sun (dated 7/20/21), Dr. Duan (dated 8/13/21), and Dr. Shin (dated 8/18/21). Comments from the team will be reflected in the final labeling and the approval letter.

Table 18: Reviewers Providing Labeling Comments and Location in this Review Document

Section	Reviewers Providing Labeling Comments & Location in this Review
1 Indications and usage	Clinical team: 7.4
6 Adverse reactions	Clinical team: 7.3.4
8 Use in specific populations	DGE- Shivangi Vachhani/Shannon Sullivan: 7.3.5 DPMH- Shamir Tuchman/Mona Khurana (Pediatrics): 9, 10.1 DPMH- Wenjie Sun/Miriam Dinatale (Maternal Health): 10.1 Pharmacology/Toxicology- Renqin Duan/Barbara Hill: Section 5 Clinical Pharmacology- Soo H Shin/Chinmay Shukla: Section 6 Clinical team: 7.3.5
12 Clinical pharmacology	Clinical Pharmacology- Soo H Shin/Chinmay Shukla: Section 6 Clinical team: Section 6, 7.3.5
13 Nonclinical toxicology	Pharmacology/Toxicology- Renqin Duan/Barbara Hill: Section 5

Source: Reviewer's Table

Pregnancy and Lactation Labeling Rule (PLLR) Conversion

In this submission, the Applicant revised Section 8 Use in Specific Populations of TOPICORT Topical Spray, 0.25% labeling to comply with the PLLR format. Support for the proposed language was based on a review of the published literature from 1926 through 2019 in BIOSIS, EMBASE, MEDLINE, and ToxFile and cases from a Pharmacovigilance Database (SD 108 dated 6/28/2019). Wenjie Sun, MD, from the Maternal Health Division of Pediatric and Maternal Health (DPMH), provided an analysis of the submitted data, confirmation of the content of the proposal through an independent review of the literature and recommendations for labeling (review dated 7/20/21).

Renqin Duan, Pharm D, Phd (Pharmacology/Toxicology) reviewed the "Nonclinical Experience" subsections and revised the content and language to conform to current FDA practice (review dated 8/13/21).

5. Warnings and Precautions

Language regarding ophthalmic adverse reactions from new class labeling changes for topical steroids was added: "Use of topical corticosteroids, including Topicort® Topical Spray, may increase the risk of posterior subcapsular cataracts and glaucoma. Cataracts and glaucoma have been reported with the postmarketing use of topical corticosteroid products *[see Adverse Reactions (6.2)]*. Avoid contact of Topicort Topical Spray with eyes. Topicort Topical Spray may cause eye irritation. Advise patients to report any visual symptoms and consider referral to an ophthalmologist for evaluation."

6.2. Postmarketing Experience

Language regarding postmarketing experience from new class labeling changes for topical steroids was added: "Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Postmarketing reports for local adverse reactions to topical corticosteroids included atrophy, striae, telangiectasias, itching, dryness, hypopigmentation, perioral dermatitis, secondary infection, and miliaria. Ophthalmic adverse reactions of cataracts, glaucoma, and increased intraocular pressure have been reported during use of topical corticosteroids."

10.2. Patient Labeling

The Applicant is not seeking an expansion of the labelling for pediatric use, therefore no new pediatric-specific proposed package insert or instructions for use were submitted.

11. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for TOPICORT Topical Spray (FDA Form 3454). Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

Table 19: Covered Clinical Study DSXS-1303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 31		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

12. Additional Analyses and Information

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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