

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208079Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	01-03-2016
From	Hon-Sum Ko
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208079
Applicant	Promius Pharma LLC
Date of Submission	04-06-2015
PDUFA Goal Date	02-06-2016
Proprietary Name / Established (USAN) names	SERNIVO Spray/betamethasone dipropionate
Dosage forms / Strength	Spray/0.05%
Proposed Indication(s)	treatment of moderate plaque psoriasis in patients 18 years of age or older
Recommended:	Approval

1. Introduction

SERNIVO (betamethasone dipropionate) Spray, 0.05% is a topical drug product for which the applicant seeks approval under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the treatment of moderate plaque psoriasis in patients 18 years of age and older, with Diprolene Lotion, 0.05% as reference product. This application is for a new dosage form of betamethasone dipropionate.

The active ingredient, betamethasone dipropionate, is a synthetic, fluorinated corticosteroid currently marketed in the United States in various dosage forms (cream, ointment and lotion) by Merck & Co., Inc. under the proprietary name “Diprolene” for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years of age and older (NDAs 19-555, 18-741 and 19-716, respectively). The indication “relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses” is broader than that of, and inclusive of plaque psoriasis.

In addition, betamethasone dipropionate is currently approved as generic products under ANDAs, also for the “relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses”. Together with clotrimazole, it is a component of the combination antifungal products Lotrisone Cream and Lotrisone Lotion. As well, betamethasone dipropionate is approved together with the vitamin D analog, calcipotriene, as combination product for topical treatment of plaque psoriasis in various dosage forms (Taclonex Ointment and Suspension, as well as Enstilar Foam). However, betamethasone dipropionate has not been marketed alone for topical treatment of plaque psoriasis as a unique indication.

A number of topical corticosteroid products have been approved with the indication for the treatment of atopic dermatitis. There are also a few topical corticosteroid products approved for the indication of treatment of plaque psoriasis (clobetasol propionate in the form of Clobex Shampoo and Clobex Spray, and desoximetasone as Topicort Spray). In addition, betamethasone dipropionate has been approved in combination with vitamin D analog for plaque psoriasis (Taclonex products and Enstilar Foam).

2. Background

Plaque Psoriasis

Plaque psoriasis is characterized by symmetrically distributed, scaly, erythematous plaques. Disease of limited extent may be effectively managed with topical treatment. There are many approved topical corticosteroids available for the treatment of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, which include plaque psoriasis. There are also several approved topical corticosteroid products, alone or as fixed combination with a vitamin D analog approved for the indication of plaque psoriasis. More severe disease may require systemic therapy, including the use of drugs such as methotrexate, cyclosporine and apremilast, as well as biologics or phototherapy.

Betamethasone Dipropionate

SERNIVO Spray, 0.05% is a new topical dosage form for the corticosteroid, betamethasone dipropionate. The availability of this active ingredient has been discussed in Section 1 of this CDTL Review.

Betamethasone is a synthetic, fluorinated corticosteroid with the moiety first approved in 1961 as an oral tablet dosage form, Celestone, and subsequently as oral syrup, topical cream, and injectable solution, but this line of products have been discontinued except for Celestone Soluspan, an injectable dosage form. Subsequently a monoester, betamethasone valerate (Valisone), and a diester, betamethasone dipropionate (Dirposone), were approved as topical dosage forms in 1967 and 1975, respectively, for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Although these product lines have been discontinued, generic versions may be available, and new dosage forms for betamethasone have been approved, such as the Diprolene products (see Section 1).

Nomenclature

The betamethasone dipropionate moiety is a diester of betamethasone and propionic acid, with the propionate portion linked to carbon at the 17 and 21 positions by covalent bonding. The diester is biologically active and has increased affinity for the glucocorticoid receptor and may enhance the duration of effect. Although the USP Nomenclature Policy recommends drugs be named leaving out the salt or ester portion, it actually refers the exclusion to “noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule”, and to the “actual charged state of the molecule in-vivo” while

retaining the active part of the molecule responsible for the physiological or pharmacological action of the drug substance. Since the complete diester molecule of betamethasone propionate is covalent-bonded and active, and the dipropionate portion has a contribution to the pharmacologic effect, we consider it important to regard betamethasone dipropionate as the active entity per se, and that the glucocorticoid moieties betamethasone-17-propionate and betamethasone derived from ester hydrolysis as its active metabolites.

Corticosteroids mediate their effects via binding to the glucocorticoid receptor which is expressed in almost every cell in the body and regulates genes controlling the development, metabolism, and immune response. Thus, they may play a role in cellular signaling, immune function, inflammation, and protein regulation. The precise mechanism of action by corticosteroids, including betamethasone dipropionate, in psoriasis is unknown.

Applicant Interactions with Agency

After holding a Pre-IND meeting with the agency in 2009, the applicant submitted IND 104,853 for betamethasone dipropionate spray, 0.05% in 2010, with the protocol for a phase 1 study on vasoconstriction. The intention was to develop a spray formulation for betamethasone dipropionate for the treatment of plaque psoriasis using the 505(b)(2) pathway. During the drug development stage, several issues were raised and the agency provided advice to resolve them, including:

- 505(b)(2) pathway
The applicant intended to use Diprolene (betamethasone dipropionate) Lotion, 0.05% as the list drug to pursue development of their product and rely on the agency's previous finding of safety on Diprolene Lotion, including nonclinical and clinical safety data. The agency advised the applicant that a clinical bridge would need to be established between their product and Diprolene Lotion. This could be done via clinical trials and clinical pharmacology studies, including evaluation of pharmacokinetic parameters and pharmacodynamics such as HPA axis suppression.
- Nonclinical and Photosafety studies
The agency noted that the 28-day repeat dose dermal toxicity study in minipigs showed severe dermal irritation and had to be stopped early. Its data revealed anti-inflammatory and immunosuppressive effects of corticosteroids. The agency concluded that a repeat of this study in another non-rodent species would not be needed.

The agency also noted that the 13-week repeat-dose dermal toxicity study in rats showed adrenal atrophy and immunosuppression, and waived the 2-year carcinogenicity study.

The agency informed the applicant that per the ICH M3(R2) Tripartite Guideline "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials

and Marketing Authorization for Pharmaceuticals”, the agency no longer recommended testing for photocarcinogenicity.

The agency waived nonclinical phototoxicity studies when the applicant provided information on the absence of absorbance in the ultraviolet-light spectrum between 290 and 700 nm. Nevertheless, the applicant conducted human photosafety studies (phototoxicity and photoallergenicity potential) despite lack of this absorbance.

- Target population

At the Pre-IND meeting in 2009, the applicant planned to study their product for moderate (b) (4)

in both phase 3 trials, the enrollment criteria only included subjects with plaque psoriasis of moderate severity.

- Time point for primary efficacy

In order to establish a clinical bridge between the applicant’s product and the listed drug, Diprolene Lotion, 0.05%, (b) (4)

The agency had advised using Diprolene Lotion according to labeled conditions, i.e., no more than 50 Gm per week and no more than 2 weeks (b) (4)

herefore, for the phase 3 trial BDS1205, the Diprolene Lotion treatment group used the active lotion for 2 weeks (according to labeling) followed by vehicle lotion for another 2 weeks.

The applicant planned on testing primary efficacy at the end of a 2-week treatment period in the phase 3 studies. The agency reasoned that since the treatment duration with the applicant’s betamethasone dipropionate spray would be 4 weeks, the primary endpoint should be analyzed at the end of a 4-week treatment period. As the phase 3 study protocol BDS1205 indicate, the Diprolene Lotion arm was included for clinical bridging for safety, and would not be analyzed for efficacy. Without using the Diprolene Lotion information to support efficacy, it is reasonable to base primary efficacy analysis on the Day 29 data instead of Day 15 data. The agency advised the applicant to use Day 29 as the time point for primary efficacy analysis more than once. Despite that, the primary analysis in the phase 3 trials was based on Day 15 data, even in Study BDS1206, which did not have a treatment arm of Diprolene Lotion.

3. CMC/Device

There are no unresolved CMC/Device issues.

- General product quality considerations

The applicant has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug substance and drug product. The CMC team has recommended approval with an expiration dating period of 24 months.

The composition of the drug product is shown in the following Table:

Table 1: Composition of SERNIVO Spray, 0.05%*

<u>Ingredients</u>	<u>Quality standard</u>	<u>% w/w</u>	<u>Function</u>
Betamethasone dipropionate	USP/EP	0.0643	Active
Sorbitan monostearate	NF	(b) (4)	
Polyoxyl 20 cetostearyl ether	NF		
Cetostearyl alcohol	NF/EP		
Mineral oil	USP		
Oleyl alcohol	NF/EP		
Propylparaben	NF		
Methylparaben	NF		
Butylated hydroxytoluene	NF/EP		
Hydroxyethyl cellulose	NF		
Purified water	USP		

* Potency expressed as betamethasone (0.05%)

It is noted that the strength of the drug product is expressed in terms of the steroid part of the active moiety, betamethasone (0.05%), although labeling also states that the betamethasone dipropionate component in the drug product would be 0.643 mg/Gm (i.e., 0.0643%). This has followed the example of the listed drug, Diprolene Lotion, 0.05%. The Diprolene formulations are labeled for 0.05% strength based on the betamethasone part of the betamethasone dipropionate molecule.

It appears that this labeling convention has been based on the assumption that the active moiety is betamethasone, while the contribution of the propionate portions of the molecule is discounted. In fact, the diester moiety is active, with the propionates enhancing the binding affinity of the molecule to the glucocorticoid receptor, and prolonging its effect (See Section 2 on nomenclature). For the current application, we follow the traditional convention in labeling product strength as 0.05%, but we recognize that without evidence to the contrary, the complete, non-hydrolyzed ester molecule, betamethasone dipropionate, is an active moiety at the target action site (skin) in plaque psoriasis.

- Facilities review/inspection

The facility review team from the Office of Facility and Process has issued an “Approval” recommendation for the facilities involved in this application. A post-approval inspection is recommended for the drug substance manufacturing facility, (b) (4) as it increases its manufacturing commitments and to verify corrections to deficiencies previously listed.

- Other notable issues
There are no notable CMC issues that would impact approval of SERNIVO Spray, 0.05%. The in vitro release test (IVRT) is being developed, and the Division of Biopharmaceutics finds that the applicant's confirmation that the method development and validation work is in progress and IVRT acceptance criterion will be established based on data generated during testing of the marketed drug product is acceptable.

4. Nonclinical Pharmacology/Toxicology

Dr. Jill Merrill, the pharmacology/toxicology reviewer, concludes that SERNIVO Spray, 0.05% is "approvable from a pharmacology/toxicology perspective."

- General Nonclinical Pharmacology/Toxicology Considerations (including pharmacologic properties of the product, both therapeutic and otherwise)
As a 505(b)(2) application, the applicant relies on FDA's findings of safety for Diprolene® Lotion, 0.05% to support the systemic safety of SERNIVO Spray, 0.05%. The applicant states in the cover letter of the original NDA submission:
 - The following table outlines the information to the approval of Sernivo Spray that is provided by reliance on the FDA's previous finding of safety for the listed drug Diprolene Lotion.

Information Provided by Reliance on FDA's Previous Finding of Safety for Diprolene Lotion (NDA 019716)

Source of Information	Information Provided e.g., specific sections of the 505(b)(2) application and labeling
Diprolene Lotion (NDA 019716)	Module 2.4 Module 2.6 Label Section 5 Label Section 8 Label Section 12.1, 12.3 Label Section 13

As the applicant has indicated above, the basis of reliance on FDA's previous findings in support of SERNIVO Spray, 0.05% is safety data of the listed drug, primarily pharmacology and toxicology data, as shown above in the Table in the cover letter.

- *This NDA has provided two independent clinical studies that included vehicle spray as control to support the clinical safety and efficacy of SERNIVO Spray, 0.05%, and established clinical bridge between SERNIVO Spray, 0.05% and the listed drug, Diprolene Lotion, 0.05%, by including Diprolene Lotion treatment group in one of the phase 3 trials as well as the HPA axis study and the vasoconstriction assay studies.*

Thus, the above Table from the cover letter adequately refers to the information of the listed drug (pharmacology/toxicology data) to be relied upon by FDA to support this application for which the applicant has not acquired the right of reference. No specific literature reference has been cited by the applicant for support, and none appears necessary in view of the well established safety profile of Diprolene Lotion, 0.05% and that of topical corticosteroids.

- Carcinogenicity/Genotoxicity

Consistent with the labeling of Diprolene Lotion, the prescribing information for SERNIVO Spray states that betamethasone was negative in bacterial and mammalian mutagenicity assays, positive in the in vitro chromosomal aberration assay, and equivocal in the in vivo mouse micronucleus assay.

The agency has waived the 2-year carcinogenicity study in rats because of adrenal atrophy and severe immunosuppression seen in the 13-week repeat-dose dermal toxicity study. In accordance to the ICH Guideline M3(R2) Tripartite Guideline “Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals”, photocarcinogenicity studies are no longer a requirement.

- Reproductive Toxicology

Also consistent with the labeling of Diprolene Lotion, the prescribing information for SERNIVO Spray states that intramuscular administration resulted in dose-related increase in fetal resorptions in rabbits and mice. Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg.

- Other Notable Issues (resolved or outstanding)

Nonclinical studies conducted by the applicant provided data consistent with corticosteroid effect:

- In a 13-week repeat dose dermal toxicity study in rats, topical administration of betamethasone dipropionate spray at dose levels up to up to 0.5 mg/kg/day in males and 0.25 mg/kg/day in females resulted in reduced body weight gain and adrenal atrophy consistent with the reported toxicological effects of synthetic corticosteroids. Based on the test article-induced immunosuppression, a waiver for 2-year dermal carcinogenicity study has been granted.
- In a 28-day dermal toxicity study in minipigs, betamethasone dipropionate spray up to 1.5 mg/kg/day in males and 1.0 mg/kg/day in females was administered. The study was terminated early due to severe dermal irritation attributed to vehicle. The clinical pathology, organ weight and microscopic changes were consistent with anti-inflammatory and immunosuppressive effects of corticosteroids. Additional dermal toxicity study in another non-rodent model has not been considered necessary.
- Betamethasone dipropionate, 0.05% spray did not elicit a delayed contact hypersensitivity response in guinea pigs nor was it a dermal or ocular irritant when tested in rabbits. The severe skin irritation in the minipig study has not been observed with other species or in clinical trials. SERNIVO Spray appears to show lower incidence of application site reactions when compared to vehicle spray, probably as a result of the anti-inflammatory effect of the corticosteroid.

The agency has waived nonclinical photosafety studies for SERNIVO Spray, as the product does not show absorbance of ultraviolet or light in the spectrum 290 to 700 nm.

5. Clinical Pharmacology/Biopharmaceutics

Dr. D. Tran, the Clinical Pharmacology Reviewer, makes this conclusion about the application: “The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 208079 acceptable pending agreement on recommended labeling changes.”

- General Clinical Pharmacology/Biopharmaceutics Considerations (including absorption, metabolism, half-life, food effects, bioavailability, drug-drug interactions, etc.)

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

Drug-drug interaction studies have not been performed for SERNIVO Spray, 0.05%.

The Clinical Pharmacology program for SERNIVO Spray, 0.05% has included three vasoconstriction assay studies and one study on HPA axis suppression. The following summarizes findings from these Clinical Pharmacology studies:

- The vasoconstriction assay studies in healthy subjects (BDS1103, BDS1204 and DFD01-CD-009) show that SERNIVO Spray, 0.05% is in the mid-range of potency. At first, a pilot study suggested the to-be-marketed formulation as being of high to mid-potency, but this was not confirmed in a second study which indicated the formulation as of low to mid-potency. A third trial with a larger number of subjects (N=80, with 80 completed) indicated it to be a mid-potent corticosteroid.
- The HPA axis suppression study (BDS1307) included 75 adult subjects with moderate to severe plaque psoriasis involving 20% to 50% of their body surface area (BSA) who were administered the cosyntropin stimulation test. SERNIVO Spray was applied twice daily for 15 or 29 days and Diprolene Lotion, 0.05% was applied twice daily for 15 days. Of the 68 subjects evaluated with cosyntropin stimulation at the end of treatment, HPA axis suppression was demonstrated in 20.8% (5 out of 24) of subjects treated with SERNIVO Spray for 15 days and 25.0% (5 out of 20) of those treated with Diprolene Lotion for 15 days, but not in subjects (0 out of 24) treated with SERNIVO Spray for 29

days. In this study, HPA axis suppression was defined as serum cortisol level ≤ 18 $\mu\text{g/dL}$ 30-minutes post-cosyntropin stimulation. In the 7 subjects with available follow-up values, all of them showed normal stimulation at follow-up.

- Pharmacokinetic evaluation was also included in the HPA axis suppression study (BDS1307) Most subjects had no measurable plasma concentration of betamethasone dipropionate (< 5.00 pg/mL), while the metabolites, betamethasone-17-propionate and betamethasone, were detected in the majority of subjects, with high variability but a trend towards greater systemic exposure at day 15 and lower exposure at day 29.
- Pathway of Elimination, and Critical Intrinsic Factors Potentially Affecting Elimination: Age, Gender, Hepatic Insufficiency and Renal Impairment
Elimination studies have not been conducted for SERNIVO Spray, 0.05%, and intrinsic factors like age, gender, liver insufficiency or kidney impairment have not been explored regarding elimination of betamethasone dipropionate applied topically.

However, as discussed above, it is well known that corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some topical corticosteroids and their metabolites are also excreted into the bile.

- Demographic Interactions/Special populations and Relevant Issues related to Clinical Pharmacology
Investigations on demographic interactions and special population studies with SERNIVO Spray, 0.05% have not been performed. The use of topical corticosteroids in steroid-responsive dermatoses has been in practice for a long time and interactions across age, gender, or other demographic characteristics have not been demonstrated for clinical pharmacology parameters.

Despite this, because of the increased surface area to mass ratio in pediatric patients, there is a potential for enhanced risk of systemic toxicity in such patients. Thus, the applicant will have a postmarketing requirement under PREA to assess HPA axis suppression by SERNIVO Spray, 0.05% in pediatric patients – see Section 10 of this review.

- Thorough QT (TQT) Study or Other QT Assessment
QT studies including TQT studies have not been conducted. Such studies can be waived because:
 - Systemic absorption of betamethasone dipropionate from topical use of SERNIVO Spray, 0.05% in plaque psoriasis is very small, and it has been demonstrated that plasma levels of this compound and its metabolites is low, with the plasma level of betamethasone dipropionate often below quantitation in the HPA axis suppression study (BDS1307) which required maximal use;

- Betamethasone and its esters including betamethasone dipropionate and betamethasone valerate have been marketed for several decades as both systemic and topical formulations without evidence of cardiac toxicity or arrhythmia induction, including QT_c prolongation; and
- The agency had indicated to the applicant that if a clinical bridge was established between SERNIVO Spray, 0.05% and the reference product, Diprolene Lotion, 0.05%, TQT studies could be waived - as this application has included studies BDS1307 (HPA axis suppression) and BDS1205 (phase 3 trial) to establish the clinical bridge between SERNIVO Spray and Diprolene Lotion, it is reasonable to waive TQT studies on this product.
- Other Notable Issues (resolved or outstanding)
There are no outstanding issues on Clinical Pharmacology besides requirement to assess HPA axis suppression potential and pharmacokinetic parameters in pediatric patients – see Section 10 of this review.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

- Background of Clinical Program
See Section 2 of this Review under “Applicant Interactions with Agency” for background of the clinical program.

The applicant had planned on developing SERNIVO Spray, 0.05% under the 505(b)(2) pathway with Diprolene Lotion, 0.05% as the reference product, for the indication of treatment of moderate (b) (4) plaque psoriasis. Diprolene Lotion, 0.05% has limitations of use, with dosing at no more than 50 Gm per week for no more than 2 consecutive weeks.

The vasoconstriction assay studies (BDS1103, BDS1204 and DFD01-CD-009) showed that SERNIVO Spray, 0.05% is of lower potency (mid-potency) than that of Diprolene Lotion, 0.05% (super-potent). The applicant subsequently planned on two phase 3 trials (BDS1205 and BDS1206) to study subjects having moderate plaque psoriasis with use of SERNIVO Spray for a period of 4 weeks. Diprolene Lotion, 0.05% was used in a treatment arm in one of the phase 3 trials for a period of 2 weeks (as per labeling) followed by vehicle lotion for an additional 2 weeks. The primary efficacy endpoint was planned at Day 15 of these studies.

- The agency did not agree on limiting the study to moderate plaque psoriasis and advised the applicant to study moderate to severe plaque psoriasis (b) (4) .

- The agency also did not agree on the primary efficacy being analyzed at Day 15 and advised using Day 29 for primary efficacy evaluation.

However, the applicant continued to include only moderate plaque psoriasis subjects in the phase 3 program and used Day 15 for primary efficacy evaluation.

Despite this, the applicant conducted an HPA axis suppression study (BDS1307) under maximal use conditions with SERNIVO Spray, 0.05% use for 15 days or 29 days in subjects having *moderate to severe* plaque psoriasis, and including a treatment group with use of Diprolene Lotion, 0.05% in subjects with same disease severity for 15 days (as per labeling). This study and the phase 3 trial which included the Diprolene Lotion treatment arm (BDS1205), primarily form the clinical bridge between SERNIVO Spray, 0.05% and the reference product, Diprolene Lotion, 0.05%.

- Basic Design of Efficacy Studies and Results

There were two phase 3 trials (BDS1205 and BDS1206) to support SERNIVO Spray, 0.05% for the treatment of moderate plaque psoriasis. They enrolled subjects age 18 and older with stable plaque psoriasis involving 10-20% body surface area not including the face, scalp, groin, axillae, and other intertriginous areas, and having an investigator’s global assessment (IGA) of ‘moderate’, which corresponds to a score of 3 on a scale from 0 to 4 at baseline. The subjects applied treatment twice daily for 28 days. One of the studies (BDS1205) also included a treatment arm for the listed drug of this 505(b)(2) application, Diprolene® Lotion, 0.05%, and a treatment arm for vehicle lotion. Subjects on the Diprolene® Lotion, 0.05% arm applied the active lotion for 14 days (as per labeling) followed by vehicle lotion for 14 days.

The two phase 3 trials enrolled a total of 671 subjects, with 356 subjects randomized to SERNIVO Spray, 0.05%, 90 subjects to Diprolene Lotion, 0.05%, and the remainder to vehicle formulations. The baseline demographics and disease severity were comparable between treatment groups in these trials. The mean age was approximately 50 years, with 13% of subjects being of age 65 and older. The majority of subjects were male (62%), white (85%), and non-Hispanic (69%).

The following analysis of primary endpoint “treatment success” (defined as IGA = 0 or 1 [0=none, 1=minimal or almost clear] and at least a 2-grade reduction from baseline) at Day 15 is according to that from the Statistical Reviewer, Dr. K. Fritsch.

Table 2: Primary endpoint analysis in Studies 1205 and 1206

	Study 1205				Study 1206	
	SERNIVO Spray N=174	Vehicle Spray N=87	Diprolene Lotion* N=90	Vehicle Lotion N=43	SERNIVO Spray N=182	Vehicle Spray N=95
Treatment Success Day 15	19.0%	2.3%	18.9%	9.3%	21.5%	7.4%
	p<0.001				p=0.002	

*Diprolene Lotion data not compared with other arms, as protocol indicates this arm is for safety data bridging.
 -P-values are for SERNIVO Spray vs. vehicle spray.
 -Treatment Success missing data are handled with multiple imputation for SERNIVO Spray and vehicle spray and LOCF for Diprolene Lotion and vehicle lotion.

The following secondary endpoint analyses are also according to those of the Statistical Reviewer, Dr. K. Fritsch.

Table 3: Secondary endpoint analysis in Studies 1205 and 1206

	Study 1205				Study 1206	
	SERNIVO Spray N=174	Vehicle Spray N=87	Diprolene Lotion* N=90	Vehicle Lotion N=43	SERNIVO Spray N=182	Vehicle Spray N=95
Treatment Success Day 29	34.5%	13.6%	21.1%	9.3%	42.7%	11.7%
	p<0.001				p<0.001	
Treatment Success Day 8	10.0%	1.2%	6.7%	2.3%	12.7%	7.4%
	p=0.003				p=0.156	
TSS ₅₀ Day 4	12.1%	2.3%	5.6%	2.3%	14.3%	10.5%
	p=0.004				Not tested	

*Diprolene Lotion data not compared with other arms, as protocol indicates this arm is for safety data bridging. For the Day 29 data, Diprolene Lotion arm used vehicle lotion for the second two weeks after initial use of Diprolene Lotion in the first 2 weeks.
 -P-values are for SERNIVO Spray vs. vehicle spray.
 -Secondary endpoints were evaluated in sequential order to control the Type I error.
 -Treatment Success missing data are handled with multiple imputation for SERNIVO Spray and vehicle spray and LOCF for Diprolene Lotion and vehicle lotion.
 -TSS₅₀ missing data are handled with baseline carried forward.

These data indicate that:

- SERNIVO Spray was superior to vehicle spray in both studies for treatment success at Day 29, the first ranked secondary efficacy endpoint.
 - For the next ranked secondary endpoint of treatment success at Day 8, superiority was only demonstrated in Study BDS1205, but not Study BDS1206.
 - For the final ranked secondary endpoint of $\geq 50\%$ reduction in Total Sign Score at Day 4, superiority was also only demonstrated in Study 1205, but was not tested in Study 1206, because sequential testing stopped after treatment success at Day 8 was not statistically significant.
- Notable Efficacy Issues Resolved and Outstanding
 Studies exploring variations in product strength or dosing frequency were not conducted. Dosing of SERNIVO Spray, 0.5% has been based on the dosing regimen for the reference product, Diprolene Lotion, 0.05% (twice daily). However, because SERNIVO Spray is of lower potency than Diprolene Lotion, the phase 3 trials have studied the efficacy of SERNIVO Spray with 2- and 4-week dosing periods (Diprolene Lotion limitation of use up to 2 weeks), both of which showed superiority over vehicle spray in the treatment of plaque psoriasis of moderate severity. As a 4-week treatment period has not been associated with additional safety issues (see Section 8 of this Review), it is reasonable to allow use of SERNIVO Spray, 0.05% for four consecutive weeks.

The agency had previously advised that the primary efficacy endpoint be analyzed at Day 29. The phase 3 trials used Day 15 for primary efficacy analysis and Day 29 for the first ranked secondary efficacy analysis. As superiority over vehicle spray was demonstrated at both time points for “treatment success” in each study,

the issue for selecting time point for primary analysis may be considered as resolved.

The agency had advised the applicant to study patients with moderate to severe plaque psoriasis. (b) (4)

(b) (4) the phase 3 trials only included patients with moderate disease (IGA score of 3), and the proposed indication for this application is “moderate” plaque psoriasis. As success in the treatment of moderate plaque psoriasis has been demonstrated in the phase 3 trials, and there are no additional risks or concerns in the safety profile (see Section 8 of this Review), it is reasonable to extrapolate use to disease of milder severity. Therefore an indication for the treatment of mild to moderate plaque psoriasis is recommended.

The significance of this application lies in the fact that SERNIVO Spray, 0.05%, if approved, will be the first betamethasone dipropionate product to be marketed as a single active ingredient for the indication of “treatment of plaque psoriasis” instead of the “relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses”, even though the reference product, Diprolene Lotion, 0.05% holds the broader indication. The applicant has chosen to rely on the reference product for safety data, but not both safety and efficacy data (see Section 4 of this review), and studied (b) (4) moderate (b) (4) after the finding of lower potency for SERNIVO Spray, 0.05% (mid-potency vs superhigh potency of Diprolene Sparay, 0.05%). Thus, it is appropriate that the indication be different from that for the reference product.

8. Safety

- Adequacy of the Database, Major Findings/Signals.

This application includes 7 phase 1 studies (3 vasoconstriction assay studies and 4 dermal safety studies) in normal subjects, one safety study on HPA axis suppression and pharmacokinetics in patients with moderate to severe plaque psoriasis, and 2 pivotal phase 3 studies in patients with moderate plaque psoriasis. A total of 477 healthy adult male and female subjects and 741 adult patients with psoriasis were included in these studies.

The safety evaluation of SERNIVO Spray, 0.05% focused on two areas: systemic glucocorticoid adverse effects and local cutaneous safety:

- Systemic glucocorticoid adverse effects include HPA axis suppression with the potential for adrenal insufficiency, iatrogenic Cushing’s syndrome, impaired glucose tolerance and other metabolic changes. None of these manifestations were observed in the phase 3 clinical trials on SERNIVO Spray, 0.05%. The study on HPA axis suppression in patients with moderate to severe plaque psoriasis under maximal use conditions provided a risk estimate for

suppression of ~21% after 15 days of twice daily use when tested with cosyntropin stimulation. No suppression was observed after 29 days of twice daily use. Diprolene Lotion, 0.05%, the reference product, showed a rate of HPA axis suppression of 25% in this study.

- The most common adverse effects (>1%) observed in the phase 3 trials were application site reactions, including pruritus, burning/stinging, pain, and skin atrophy. However, pruritus and pain are also manifestations of psoriasis, and the vehicle spray appeared to be associated with a greater proportion of subjects showing these effects. Since SERNIVO Spray is a topical corticosteroid product which has anti-inflammatory effects, this safety profile may be reasonably anticipated. Dermal safety studies on irritancy, sensitization, phototoxicity, and photoallergenicity did not yield positive evidence for the potential of SERNIVO Spray, 0.05% to cause these phenomena.

There were no deaths or serious adverse events considered related to treatment in the phase 3 clinical trials for SERNIVO Spray, 0.05%. Five (5) subjects discontinued treatment but none of the discontinuations was considered to be related to treatment with SERNIVO Spray, 0.05%. Vital sign observations during the clinical trials did not indicate any clinically significant changes. Routine clinical laboratory testing and ECG studies were not conducted in the clinical development program because clinically meaningful changes were not anticipated from use of a topical corticosteroid product containing betamethasone dipropionate.

In conclusion, the clinical program involved studies in adults and the data thus far suggest an acceptable safety profile. The applicant will have a postmarketing requirement to conduct a study on HPA axis suppression and pharmacokinetics in adolescents with plaque psoriasis in order to ascertain safety in this pediatric population.

- Notable Safety Issues Resolved or Outstanding
There are no special safety issues. The risk of HPA axis suppression is common to glucocorticoid products, including topical corticosteroids. In this application, the applicant has demonstrated a risk for HPA axis suppression in the order of approximately 21% when SERNIVO Spray, 0.05% was under maximal use conditions for 15 days in moderate to severe plaque psoriasis but no suppression after use for 29 days. In addition, the risks for local adverse reactions including skin atrophy are common across topical corticosteroids, and appear to be low in the phase 3 clinical trials.

9. Advisory Committee Meeting

Betamethasone dipropionate is not a new molecular entity. It is a biologically active diester of betamethasone, and has been marketed as topical corticosteroid in various

dosage forms to treat dermatologic indications for over 40 years. SERNIVO Spray, 0.05%, is a new formulation for betamethasone dipropionate, with safety profile similar to that of marketed topical corticosteroid products. Its clinical trials have consistently demonstrated efficacy in the treatment of plaque psoriasis.

Therefore, no advisory committee meeting was convened for discussion on this application.

10. Pediatrics

- Extrapolation of Efficacy

Efficacy for the treatment of patients 12 years to 16 years 11 months can be extrapolated from adult efficacy data for SERNIVO Spray, 0.05%. Plaque psoriasis in adolescents is similar to disease in adults. No differences in response to treatment is anticipated. Extrapolation for efficacy has also been used for extending treatment to the adolescent age group for the listed drug, Diprolene Lotion, 0.05% and other topical corticosteroids.

- PeRC Review Outcome-PMCs, Deferrals, Waivers, Pediatric plan, Peds Assessment

The agency has accepted the applicant's iPSP after presentation to PeRC and discussion in 2014.

In this iPSP, the applicant has proposed waiver for pediatric assessment in the age group 0 to 11 years 11 months. The iPSP also proposed deferral of a safety/pharmacokinetic study with evaluation of HPA axis suppression and plasma levels of betamethasone dipropionate and its metabolites in the age group 12 years to 16 years 11 months, because the adult indication would be ready for approval.

In this application, the applicant has included requests for partial waiver and deferral under PREA as per the accepted iPSP. These requests have been discussed at a PeRC meeting in December, 2015, and PeRC agreed to the requests for waiver and deferral.

For the deferred study, the study protocol has been submitted by June 30, 2015 and initiated by July 31, 2015, with estimated completion date of March 31, 2018 and submission of study report by July 31, 2018.

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP)
Not applicable

- Exclusivity or Patent Issues of Concern
No issues of concern
- Financial Disclosures
Applicant has adequately presented financial disclosure information in Form 3454.
- Other GCP Issues
None
- OSI Audits
Clinical Investigator site audits have been waived, as no single Investigator site carried sufficient weight to impact the outcome of each of the phase 3 trials, BDS1205 or BDS1206. Also, betamethasone dipropionate products have been marketed for many years with clinical trials on such products reviewed by the agency such that the safety and efficacy profiles are well established; the profiles for SERNIVO Spray, 0.05% are consistent with those of the marketed products.
- Other Outstanding Regulatory Issues.
None

12. Labeling

Labeling negotiations are ongoing at the time of completion of this CDTL Review. The agency has accepted the proprietary name SERNIVO Spray, and the applicant has accepted the indication to treat plaque psoriasis of mild to moderate severity (b) (4)

Final labeling will be attached to the Approval Letter.

The prescribing information follows the format and content of most topical corticosteroid labels under the Physician Labeling Rule (PLR). As this application was submitted prior to the Pregnancy and Lactation Labeling Rule (PLLR) coming into effect on June 30, 2015, the applicant has chosen to maintain Section 8 of the prescribing information under original PLR format at this time, and have conversion to PLLR format completed before June 30, 2019.

The draft label contained an Instructions-For-Use (IFU) brochure, but did not include a patient package insert (PPI). Upon advice from the agency, the applicant has submitted a draft PPI, which is also currently under labeling negotiation. There are no major outstanding issues for the IFU or the PPI.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval for treatment of mild to moderate plaque psoriasis in patients 18 years of age or older

- Risk Benefit Assessment

This application has demonstrated success in the treatment of plaque psoriasis of moderate severity in adults with SERNIVO Spray, 0.05% twice daily for 2 weeks and 4 weeks in two phase 3 trials, in the order of approximately 20% and 40%, respectively.

This application has also demonstrated that SERNIVO Spray, 0.05% use may be associated with systemic and local adverse effects common to topical corticosteroids, including HPA axis suppression (21% under maximal use conditions for 2 weeks, and 0% for 4 weeks) and skin atrophy.

On balance, it is acceptable to use SERNIVO Spray, 0.05% in the treatment of mild to moderate plaque psoriasis at a twice daily regimen for up to 4 weeks.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Risks be managed with product labeling and routine pharmacovigilance; Risk Evaluation and Mitigation Strategy (REMS) not considered to be necessary

- Recommendation for other Postmarketing Requirements and Commitments

Postmarketing requirement (PMR) under PREA as per iPSP accepted on December 4, 2014:

Pediatric assessment of HPA axis suppression under maximal use conditions in adolescents 12 years to 16 years 11 months of age having plaque psoriasis, and evaluation of their pharmacokinetic parameters, with these recommended timelines:

- Final Protocol Submission: 06-30-2015
- (b) (4)
- Final Report Submission: 07-31-2018

As per iPSP accepted on December 4, 2014, a waiver for pediatric assessment of the age group 0 years to 11 years 11 months is recommended.

- Recommended Comments to Applicant

None

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

/s/

HON SUM KO
01/04/2016