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APPLICATION NUMBER:

208079Orig1s000

SUMMARY REVIEW

Decisional Memorandum to the File

Date:	January 6, 2016
From:	Kendall A. Marcus, M.D. Director, Division of Dermatology and Dental Products
Subject:	Summary and Recommendations
NDA #:	208079 Promius Pharma, LLC
Submission Date **PDUFA Goal**	April 6, 2015 February 6, 2016
Proprietary / Generic (USAN) names	SERNIVO Spray/betamethasone dipropionate
Dosage forms / strength	Spray, 0.05%
Proposed Indication(s)	Moderate plaque psoriasis

1. Introduction

Psoriasis is a chronic inflammatory skin disease characterized by patches of red, itchy, and scaly abnormal skin. Plaque psoriasis is the most common type, with other less common types characterized as guttate, inverse, pustular, and erythrodermic. The pathogenesis of psoriasis involves the abnormal regulation of the cells of the immune system (white blood cells including T lymphocytes, neutrophils, and other leucocytes) prompted by both environmental and genetic factors, which leads to a dysregulation of normal keratinocyte proliferation and an increase in proinflammatory cell signals. Psoriasis is likely a genetic disease with cycles of inflammation and cellular proliferation typically resulting in clinical skin plaques. There is no curative therapy.

Limited plaque psoriasis responds well to topical corticosteroids and emollients. Alternative localized therapies include vitamin D analogs, such as calcipotriene and calcitriol, tar, and topical retinoids, such as tazarotene. Localized phototherapy is another option. Combinations of topical corticosteroids and either calcipotriene, calcitriol, tazarotene or UVB phototherapy may prescribed by dermatologists.

2. Background

Betamethasone dipropionate is a fluorinated corticosteroid that has been FDA approved for the treatment of psoriasis, atopic dermatitis and other inflammatory skin diseases since 1975. It is an active diester moiety with increased affinity for the glucocorticoid receptor over that of betamethasone, which together with betamethasone-17-propionate, constitutes the active metabolites of betamethasone dipropionate upon hydrolysis.

The applicant is seeking approval for SERNIVO (betamethasone diproprionate) Spray, 0.05%, through a 505(b)(2) regulatory pathway with Diprolene® Lotion (augmented

betamethasone diproprionate), NDA 19716 (Merck Sharp Dohme, approved August 1,1988) as the listed drug. According to the applicant, the spray dosage is convenient for patients to use and dries completely, leaving no sticky residue. Betamethasone dipropionate at the same 0.05% strength is commercially available in cream, ointment, and lotion formulations. The proposed indication is for treatment of moderate plaque psoriasis in patients 18 years of age and older. The proposed dosing regimen is to shake well, apply to the affected area and rub in gently twice a day for up to 4 weeks.

This application is significant because betamethasone dipropionate products have been marketed alone for the indication of relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses or in combination for the treatment of plaque psoriasis, but not as a single-active ingredient product for plaque psoriasis. Several glucocorticoid products are approved for plaque psoriasis but not corticosteroid-responsive dermatoses; SERNIVO Spray, 0.05% would be the first betamethasone dipropionate product with a unique psoriasis indication.

The clinical study data for SERNIVO Spray, 0.05% consists of 10 clinical trials with SERNIVO Spray, 0.05%: 7 Phase 1 studies (three vasoconstrictor assay studies and four safety studies of cumulative irritation, phototoxicity, photoallergy and sensitization), a Phase 2 hypothalamic-pituitary-adrenal (HPA) axis suppression and pharmacokinetic (PK) trial and two Phase 3 double-blind trials evaluating safety and efficacy in subjects with moderate plaque psoriasis. All 10 clinical trials were conducted with the final to-be marketed formulation. The listed drug, Diprolene® (augmented betamethasone dipropionate) Lotion, 0.05%, was included for comparison in the Phase 1 vasoconstrictor studies, the Phase 2 HPA axis suppression trial and one of the Phase 3 safety and efficacy trials in order to construct a clinical bridge to the Agency's findings of safety for this approved product.

3. CMC

The quality sections of this NDA were reviewed by a CMC team (Drug substance Reviewer: Sam Bain, Ph.D., Drug product Reviewer: Hamid Shafiei, Ph.D., Biopharmaceutics Reviewer: Vidula Kolhatkar, Ph.D., Process Reviewer: Yaodong Huang, Ph.D., Micro Reviewer: Erika Pfeiler, Ph.D., Facility Reviewer: Tony Wilson, Ph.D.) under the technical leadership of Yichun Sun, Ph.D., with the recommendation for approval. The applicant of this NDA provided sufficient CMC information to assure the identity, purity, strength and quality of the drug substance and drug product. The facility review team from the Office of Facility and Process has issued an "Approval" recommendation for the facilities involved in this application. Although no IVRT data were submitted, adequacy of the proposed IVRT method and the proposed in vitro release acceptance criteria will not affect approvability.

The drug product is betamethasone dipropionate lotion co-packaged with a manual spray pump for installation by the pharmacist prior to dispensing. The formulation composition of SERNIVO Spray, 0.05% is shown in Table 1.

Table 1 – Formulation composition of SERNIVO Spray, 0.05%

S.No	Ingredients	Betamethasone Dipropionate Spray, 0.05%*
		%w/w
1	Betamethasone dipropionate USP, EP	0.0643
2	Sorbitan monostearate NF,	(b) (4)
3	Polyoxyl 20 cetostearyl ether, NF,	
4	Cetostearyl alcohol NF/EP,	
5	Mineral oil USP,	
6	Oleyl alcohol NF	
7	Propylparaben, NF	
8	Methylparaben, NF	
9	Butylated hydroxytoluene, NF/EP	
10	Hydroxyethyl cellulose, NF,	
11	Purified Water, USP/EP	

*Potency expressed as betamethasone

4. Nonclinical Pharmacology/Toxicology

Please refer to the review prepared by Jill Merrill, Ph.D., the Pharmacology/Toxicology reviewer for complete details. Dr. Merrill finds this application approvable from the pharmacology/toxicology perspective.

The sponsor is relying on FDA's findings of safety for Diprolene® Lotion to support the systemic safety of SERNIVO Spray, 0.05%. 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. It caused a 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.

The sponsor conducted repeat-dermal toxicity studies with betamethasone dipropionate in both rodents and nonrodents. In a 13-week toxicity study in rats, topical administration of betamethasone dipropionate at dose concentrations of 0.05% and 0.1% (providing dose levels 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 the sponsor was granted a waiver for conduct of a 2-year dermal carcinogenicity study.

A 28-day dermal toxicity study was conducted in minipigs with daily topical administration of 0.05% and 0.1% betamethasone dipropionate (providing dose levels up to 1.5 mg/kg/day in males and 1.0 mg/kg/day in females). Although this study was terminated early due to severe dermal irritation attributed to the vehicle, clinical

pathology, organ weight and microscopic changes in the treated animals were consistent with the anti-inflammatory and immunosuppressive effects of corticosteroids.

An additional dermal toxicity study in an alternate nonrodent model is not considered necessary. SERNIVO Spray, 0.05% did not elicit a delayed contact hypersensitivity response in guinea pigs nor was it a dermal or ocular irritant when tested in rabbits.

5. Clinical Pharmacology

Please refer to the review completed by Doanh Tran, Ph.D., the clinical pharmacology reviewer for complete details. This application is approvable from the clinical pharmacology perspective.

PK/HPA axis suppression:
The systemic exposure of SERNIVO Spray, 0.05% and Diprolene® Lotion, 0.05% was compared using HPA axis suppression as a surrogate endpoint and sparse pharmacokinetic sampling at 1, 3 and 6 hours after application. Plasma cortisol was determined before and after adrenocorticotropic hormone (ACTH) stimulation in subjects with moderate to severe plaque psoriasis treated twice daily with SERNIVO Spray, 0.05% (for 15 or 29 days) or Diprolene® Lotion, 0.05% (for 15 days).

The incidence of HPA axis suppression was similar between the SERNIVO Spray, 0.05% and Diprolene® Lotion, 0.05% 15-day groups at 20.8% (5/24) and 25.0% (5/20), respectively. HPA axis suppression was not observed in the SERNIVO Spray, 0.05% 29-day group (0 of 24). Seven of 10 suppressed subjects with follow-up results had returned to normal.

The majority of subjects in all groups had no measurable betamethasone dipropionate plasma concentrations (<5.00 pg/mL) at most time points just before and after the last application of study product at the End-of-Treatment visit. In contrast, betamethasone dipropionate metabolites (i.e., betamethasone-17-propionate and betamethasone) were detected in the majority of subjects. Therefore, the bioavailability analysis focused on the metabolites concentrations.

Plasma concentrations at 0, 1, 3, and 6 hours appearto be at a plateau on Day 15 and Day 29. On Day 15 the SERNIVO Spray, 0.05% had similar mean Cmax for betamethasone-17-propionate and betamethasone compared to Diprolene® Lotion.

Potency classification:
The corticosteroid potency of SERNIVO Spray, 0.05% was compared to the listed drug, Diprolene® Lotion, 0.05% and other corticosteroids of known potency in three studies using the vasoconstrictor method. One pilot trial suggested the to-be-marketed formulation was ranked as high to mid-potent. A follow-up trial to confirm potency did not show consistent results with the pilot trial and ranked it as low to mid-potent. A third trial was conducted in a larger number of subjects (n=78 completers) to resolve the discrepancy. The results indicated it is a mid-potent corticosteroid.

The three vasoconstrictor studies all demonstrated that SERNIVO Spray, 0.05% is of lower potency compared to the listed drug, Diprolene® Lotion, 0.05%.

6. Clinical/Statistical

Please refer to the reviews completed by Hon Sum Ko, M.D., the clinical reviewer and Kathleen Fritsch, Ph.D., the biostatistical reviewer for full details. Both reviewers find this application approvable from an efficacy perspective.

To support an efficacy claim for SERNIVO Spray, 0.05% for the treatment of moderate psoriasis, the applicant conducted two trials. Studies 1205 and 1206 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 an investigator's global assessment (IGA) of 'moderate', which corresponds to a score of 3 on a scale from 0 to 4. Subjects applied treatment twice daily for 28 days. One of the studies 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 lotion for 14 days followed by vehicle lotion for 14 days, because Diprolene® Lotion, 0.05% is only labeled for 14 days use.

Baseline demographics were generally balanced across the treatment groups in the two studies. The mean age was approximately 50 years, with 13% of subjects age 65 and older. The majority of subjects were male (62%), white (85%), and non-Hispanic (69%).

Both studies had statistically significant results for the primary efficacy endpoint of treatment success [clear or almost clear (0 or 1) on the IGA with at least 2 grades reduction from baseline] at Day 15 for SERNIVO Spray, 0.05% versus vehicle spray ($p \leq 0.002$). The secondary endpoints were assessed in sequential order. The first ranked secondary endpoint of treatment success at Day 29 was also statistically significant in both studies ($p < 0.001$). Thus, efficacy has been established for treatment success at Days 15 and 29. Treatment effects were generally consistent across gender and race.

Table 1, excerpted from Dr. Fritsch's review, summarizes the efficacy results from Studies 1205 and 1206.

Table 1 – Efficacy Results in Study 1205 and 1206

	Study 1205				Study 1206	
Primary	Beta Spray N=174	Vehicle Spray N=87	Beta / Veh Lotion N=90	Vehicle Lotion N=43	Beta Spray N=182	Vehicle Spray N=95
Trt Succ. at Day 15	19.0%	2.3%	18.9%	9.3%	21.5%	7.4%
	p<0.001				p=0.002	
Secondary						
Trt Succ. at Day 29	34.5%	13.6%	21.1%	9.3%	42.7%	11.7%
	p<0.001				p<0.001	
Trt Succ. at Day 8	10.0%	1.2%	6.7%	2.3%	12.7%	7.4%
	p=0.003				p=0.156	
TSS50 at Day 4	12.1%	2.3%	5.6%	2.3%	14.3%	10.5%
	p=0.004				Not tested	

-P-values are for bethamethasone 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 betamethasone spray and vehicle spray and LOCF for betamethasone lotion and vehicle lotion.
-TSS50 missing data are handled with baseline carried forward.

7. Clinical/Safety

As previously described, this application consists of 10 clinical trials with SERNIVO Spray, 0.05%: 7 Phase 1 studies (three vasoconstrictor assay studies and four safety studies of cumulative irritation, phototoxicity, photoallergy and sensitization), a Phase 2 hypothalamic-pituitary-adrenal (HPA) axis suppression and pharmacokinetic (PK) trial and two Phase 3 double-blind trials evaluating safety and efficacy in subjects 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 systemic glucocorticoid adverse effects and local cutaneous safety. Topical corticosteroid use carries with it the potential for systemic glucocorticoid adverse effects. These 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 about 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, 0.05% 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. The SERNIVO Spray drug product does not show absorbance in the ultraviolet or visible light spectrum, and would not be expected to induce phototoxic or photoallergenic reactions.

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.

8. Advisory Committee Meeting

No advisory committee was held as this application did not raise any novel or difficult issues for which the Agency would wish to seek outside advice or discussion.

9. Pediatrics

Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk for systemic adverse effects with use of topical corticosteroids, including betamethasone dipropionate.

The applicant requested a deferral of pediatric studies for subjects 12 years to 16 years 11 months of age. There is an agreed initial pediatric study plan (iPSP) dated December 4, 2014. As per the agreed iPSP, the applicant will conduct a PK/HPA axis suppression trial in adolescents aged 12 years to 16 years 11 months with plaque psoriasis. This trial will be included as a PREA postmarketing requirement. A waiver will be granted for studies in pediatric patients<12 years of age in the agreed iPSP, as the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients below 12 years of age.

10. Other Relevant Regulatory Issues

No issues related to financial disclosures or patent issues were identified in the review of the application. The review team did not recommend that the Office of Scientific Investigations (OSI) conduct inspections for psoriasis trials for a product that was already approved and available on the U.S. market.

11. Decision/Action/Risk Benefit Assessment

Recommended regulatory action: Approval

I concur with the recommendations of the multi-disciplinary review team regarding approval of NDA 208079, SERNIVO (betamethasone dipropionate) Spray, 0.05% for the treatment of mild to moderate plaque psoriasis with twice daily dosing for up to 4 weeks.

Risk-benefit assessment: The applicant established the efficacy and safety of SERNIVO Spray, 0.05% in two adequate and well-controlled trials with twice daily use in moderate plaque psoriasis for 4 weeks and provided sufficient information in their application to support product labeling. Although the listed drug, Diprolene Lotion, 0.05% has duration of use limited to 2 weeks, the robust efficacy of SERNIVO Spray, 0.05% over the 4-week treatment period justifies the modest risks, the most significant of which appears to be the risk for local skin reactions and HPA axis suppression, especially when suppression was not observed at the end of a 4-week period of treatment under maximal use conditions.

In addition, the treatment success in moderate plaque psoriasis can be extrapolated to plaque psoriasis of mild severity, which may incur more limited exposure to corticosteroid effects due to lower extent of skin area involvement and/or more rapid response. The risk-benefit balance is also in favor of including the approval to a broader severity spectrum – mild to moderate plaque psoriasis.

Postmarketing Risk Evaluation and Management Strategies: Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) will not be required.

Postmarketing requirements (PMR) and commitments (PMC): The applicant will be required to conduct the following PREA PMR,

- A trial evaluating the adrenal suppression potential and pharmacokinetic properties of twice daily betamethasone dipropionate spray, 0.05% under maximal use conditions in subjects 12 years to 16 years 11 months of age with plaque psoriasis.

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/s/

KENDALL A MARCUS
01/06/2016