CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208183Orig1s000

SUMMARY REVIEW

CDTL and Summary Review for Regulatory Action

Date	6 November 2015
From	Jill A Lindstrom, MD
Subject	Deputy Director Summary Review
NDA #	208183
Applicant Name	Ferndale Laboratories, Inc.
Date of Submission	23 December 2014
PDUFA Goal Date	6 November 2015
Proprietary Name	Ultravate
Established (USAN) Name	Halobetasol propionate
Dosage Forms / Strength	Lotion, 0.05%
Proposed Indication	Treatment of plaque psoriasis in patients 18 years of age and older
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brenda Carr, MD
Statistical Review	Kathleen Fritsch, PhD
Pharmacology Toxicology Review	Jill Merrill, PhD
CMC Review/OBP Review	Sam Bain, PhD; Hitesh Shroff, PhD; Xueli Zhu, Phd: Neal Sweeney, PhD; Denise M. DiGiulio, RPh; Vidula Kolhatkar, PhD
Clinical Pharmacology Review	Doanh Tran, PhD
OPDP	Tara Turner, PharmD, MPH
OSI	Roy Blay, PhD
OSE/DMEPA	Carlos Mena-Grillasca, RPh
Labeling	Nancy Xu, MD
DPMH/Maternal Health Team	Leyla Sahin, MD
Project Management	Cristina Attinello, MPH

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DPMH=Division of Pediatric and Maternal Health

1. Introduction

Ultravate (halobetasol propionate) lotion, 0.05% is a topical drug product for which the applicant seeks approval under Section 505 (b)(1) of the Federal Food Drug and Cosmetic Act for the topical treatment of plaque psoriasis in patients 18 years of age and older. The active ingredient, halobetasol propionate, is marketed in the United States in cream and ointment

dosage forms for treatment of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses. The applicant submitted a letter of authorization to reference the NDAs for Ultravate cream and ointment.

This memo summarizes the findings of the multidisciplinary review team, serves as both the CDTL (a role I fulfilled during the review cycle) and Summary review, and provides the rationale for my decision.

2. Background

Psoriasis is chronic inflammatory disease characterized by circumscribed erythematous, scaly plaques on the skin. Sites of predilection include scalp, sacrum, umbilical area, and extensor surfaces of the limbs. Involvement is typically symmetrical. As a result of the isomorphic response (Koebner's phenomenon), lesions may appear at sites of minor trauma, such as the elbows and knees. Associated comorbidities include psoriatic arthritis, other autoimmune inflammatory diseases, coronary artery disease, metabolic syndrome, obesity and depression. Topical treatment is used for patients with limited disease or for those with more widespread disease who do not want to undergo phototherapy or systemic therapy. Topical therapeutic options include corticosteroids, available in a range of potencies, strengths, and dosage forms, vitamin D analogs, tazarotene, and combination of calcipotriene and betamethasone dipropionate.

Halobetasol propionate is a synthetic (b) (4) corticosteroid that is marketed for topical use in cream and ointment dosage forms. This application is for a lotion dosage form of the same strength as the ointment and cream dosage forms and indicated for plaque psoriasis.

The applicant participated in an EOP2 meeting on 25 July 2012 and a preNDA meeting on 27 October 2014.

3. CMC/Device

The drug substance, halobetasol propionate, is an off-white crystalline powder with a molecular weight of 484.96 and a molecular formula of $C_{25}H_{31}ClF_2O_5$. The drug product, Ultravate (halobetasol propionate) lotion, 0.05%, is an (b) (4) which is white in color. The composition is described in the following table:

Ingredient	Function	Composition (%w/w)
Halobetasol propionate, USP	Active ingredient	0.05
Diisopropyl adipate	(b) (4)	
Octyldodecanol, NF		
Ceteth 20 (b) (4) (b) (4)		
Poloxamer 407 NF		
Cetyl alcohol, NF		
Stearyl alcohol, NF		
Propylparaben, NF		
Butylparaben, NF		
Glycerin, USP		
Carbomer homopolymer, NF		
Propylene glycol, USP		
Sodium hydroxide, NF (b) (4)		
(b) (4) water, USP		

Source: Adapted from NDA 208183 section 2.3.P.1, p1.

There are no novel excipients. The product, which contains water, is formulated with propylparaben and butylparaben to provide (b) (4). Microbial limits test is included in the finished product specifications.

The drug product is packaged into 2 ounce white oval tapered high density polyethylene bottles with polypropylene disc top caps, as well as (b) (4) (b) (4) with polypropylene caps (sample). Stability data support an expiry of 24 months.

The facility review team from the Office of Process and Facilities completed facilities inspections and issued an overall "Acceptable" recommendation.

The CMC lead reviewer, Dr. Yichun Sun, concluded that the applicant provided sufficient information to assure the identity, strength, purity and quality of the drug product, and did not recommend any postmarketing commitments.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

The applicant referenced NDA 19967 Ultravate cream for data in from a battery of nonclinical studies to suport the nonclinical systemic safety of halobetasol propionate. The applicant submitted data from a 13-week dermal toxicity study in rats and a 4-week dermal toxicity study in minipigs, both conducted with their proposed product. Nonclinical toxicology

findings were consistent with exposure to corticosteroids, including adrenal atrophy and immune suppression. Halobetasol was found to be teratogenic in rats and rabbits and embryotoxic in rabbits. These findings are addressed in labeling.

The pharmacology/toxicology reviewer, Dr. Jill Merrill, recommended *Approval* of this application from a pharmacology/toxicology perspective; she did not identify the need for any nonclinical postmarketing commitments or requirements.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Ultravate (halobetasol dipropionate) lotion, 0.05%, is a topical corticosteroid product for the treatment of plaque psoriasis that is intended to be applied as a thin layer to the affected skin (excluding face, scalp and intertriginous areas) twice daily for up to two weeks, with the total dose not to exceed 50 grams per week.

The to-be-marketed formulation was used in all of the clinical trials, including the maximal use pharmacokinetic (PK) and hypothalamic pituitary adrenal (HPA) axis suppression study and the pivotal trials.

The applicant conducted Study 202, a comparative, parallel-group, multi-center study conducted under maximal use conditions in 43 adults subjects with moderate to severe plaque psoriasis with at least 20% body surface area (BSA) involvement, to evaluate the adrenal suppression potential and the PK properties of Ultravate lotion versus Ultravate cream. Study drug was applied twice daily for up to two weeks. Cosyntropin stimulation testing was performed at screening (at least 4 weeks before projected end of treatment) and at end-of-treatment. Five of 20 subjects (25%) treated with Ultravate lotion and 3 of 21 subjects (14.3%) treated with Ultravate cream demonstrated adrenal suppression, defined as a 30-minute post-stimulation cortisol level of $\leq$18 mcg/dL. In addition, at selected sites (24 subjects, 12 in each arm), blood samples for PK analysis were collected at baseline and then immediately prior to study drug administration and at hours 1, 2, 4, 6, 8, 12, and 24 hours on day 8 (subjects withheld application of drug until the 24 hour post dose sampling was completed) and again prior to study drug administration on day 15. Plasma concentrations of halobetasol propionate were detectable in all subjects. For halobetasol propionate, the mean ($\pm$standard deviation) value for C_{max} was 201.1 ($\pm$157.5) pg/mL, and for AUC_{τ} was 1632 ($\pm$1147) pg-h/mL. The HPA axis suppression and PK data are addressed in labeling.

The applicant conducted a single-point vasoconstrictor assay (VCA) study which included Ultravate cream and triamcinolone acetonide cream, 0.5%, as comparators. Ultravate lotion was found to be of similar potency to Ultravate cream and higher potency than triamcinolone acetonide cream, making it super-potent based on the VCA.

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The Clinical Pharmacology reviewer, Dr. Doanh Tran, found the application acceptable, and recommended a postmarketing requirement to conduct a trial to evaluate the adrenal suppression potential and PK properties of Ultravate lotion under maximal use conditions in subjects 12 years to 16 years 11 months of age with plaque psoriasis.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

The applicant submitted data from two pivotal trials, Study 304 and Study 305, to establish the effectiveness of their product in the treatment of plaque psoriasis in adults. These two studies, identical in design, were multi-center, randomized, double-blind, vehicle-controlled, parallel group studies with two arms. The trials enrolled 443 adult subjects with plaque psoriasis with an Investigator Global Assessment (IGA) score of at least 3 (moderate) and involvement of 2 to 12 percent of their body surface area. Subjects applied study drug twice daily to all psoriatic plaques except those on the face, scalp, groin, axillae and intertriginous areas for two weeks. Efficacy assessment were performed at baseline, day 8 and day 15. The primary efficacy endpoint was IGA "treatment success," defined as a score of 0 (clear) or 1 (almost clear) and a 2-grade improvement from baseline on the IGA. Secondary endpoints included "treatment success," similarly defined, on the individual signs of psoriasis (erythema, scaling, plaque elevation).

The applicant was granted a Special Protocol Assessment (SPA), and an Agreement letter was issued on 5 December 2012. Agreements included:

- General study design
- Dose regimen: halobetasol propionate lotion, 0.05%, or vehicle lotion, applied twice daily to all psoriatic plaques except those on the face, scalp, groin, axillae or intertriginous areas
- Study population: adults with plaque psoriasis involving a minimum of 2% BSA and a score of 3 or greater of the IGA
- Subject assessments on baseline/day 1, day 8 and day 15
- Primary endpoint: proportion of subjects with "treatment success" defined as an IGA score of 0 (clear) or 1 (almost clear) and at least 2 grade improvement from baseline
- Secondary endpoints: proportion of subjects with "treatment success" (clear or almost clear and at least 2 grade improvement from baseline) on individual signs of erythema, scaling and plaque elevation
- Safety assessments
- Use of Cochran-Mantel-Haenszel test stratified by analysis centers
- Use of multiple imputation for missing data

The results of the primary efficacy endpoint are presented in the following table:

	Study 304		Study 305	
Primary	Ultravate lotion N=110	Vehicle N=111	Ultravate lotion N=110	Vehicle N=112
0 or 1 on IGA	49 (44.5%)	7 (6.3%)	49 (44.5%)	8(7.1%)
	p<0.001		p<0.001	
Secondary				
0 or 1 for scaling	61 (55.5%)	12 (10.8%)	65 (59.1%)	11 (9.8%)
0 or 1 for erythema	40 (36.4%)	8 (7.2%)	48 (43.6%)	12 (10.7%)
0 or 1 for plaque elevation	50 (45.5%)	9 (8.1%)	48 (43.6%)	9 (8.0%)

Source: adapted from Statistical Review and Evaluation, NDA 208183, Kathleen Fritsch, PhD, archived 9/3/2015, p.3.

In Study 304 and Study 305, Ultravate lotion was superior to vehicle for the primary endpoint of treatment success on the IGA, as well as on the secondary endpoints of treatment success on the scales for scaling, erythema and plaque elevation.

The reader is referred to the biostatistical and clinical reviews by Kathleen Fritsch, PhD, and Brenda Carr, MD, respectively, for detailed review of the pivotal trials and additional analyses.

I concur with Drs. Fritsch and Carr that the clinical trial data support a determination of efficacy.

8. Safety

Two hundred and seventy seven subjects with psoriasis were exposed to Ultravate lotion (at the conditions of proposed labeling, hereafter the safety population) during the development program, including 220 subjects in the pivotal trials. For these subjects, the mean duration of exposure was 14.6 days (median 15 days) and the mean amount used was 72 grams (median 67 grams).

One death was reported during the development program: a 46 year old male enrolled in the contact sensitization study died of an apparent heroin overdose, which was considered unrelated to study drug administration. One subject in the safety population experienced a serious adverse event (SAE): a 69 year old male was hospitalized for an exacerbation of chronic obstructive pulmonary disease, which was considered unrelated to study drug administration.

Adverse events occurred more frequently in the safety population treated with Ultravate lotion (12%) than in those subjects treated with vehicle lotion (6%). Adverse reactions that occurred at a rate greater than 1% in the safety population treated with Ultravate lotion and at a higher rate than in the corresponding vehicle group include telangiectases (identified by active assessment), application site atrophy and headache.

Suppression of the HPA axis, a safety concern with halobetasol propionate, is discussed in section 5 of this review, and addressed in labeling.

The reader is referred to the clinical review by Dr. Brenda Carr for a full discussion of the safety database.

9. Advisory Committee Meeting

No advisory committee meeting was held, as the application did not present novel issues which merited advisory committee input. Halobetasol dipropionate has been approved in ointment and cream topical dosage forms since 1990.

10. Pediatrics

The applicant submitted safety and efficacy data obtained from adult subjects.

The applicant requested partial pediatric waiver for children aged 0 to 11 years on the basis tha (b) (4) (b) (4) and ii) the drug does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a significant number of pediatric patients in the relevant age group. The applicant requested a deferral of pediatric studies in adolescents aged 12 to 17 years because adult studies are completed and ready for approval. (b) (4) (b) (4) (b) (4) The application was presented to the Pediatric Review Committee (PeRC) on July 15, 2015; PeRC agreed with the applicant's request for waiver of studies in children 0 to 11 years of age and deferral of study in adolescents.

(b) (4)

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations conducted inspections at two clinical trial sites. No issues were identified at either site that would preclude reliance on the data that was generated.

There are no other unresolved regulatory issues.

12. Labeling

All components of labeling were reviewed.

Ultravate (halobetasol propionate) lotion, 0.05% is indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older, (b) (4) (b) (4)

Professional labeling conforms to the standards of the Physicans Labeling Rule and the Pregnancy and Lactation Labeling Rule.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval

I concur with the recommendations of the multi-disciplinary review team regarding approval of NDA 208183 Ultravate (halobetasol propionate) lotion, 0.05% for the topical treatment of plaque psoriasis in patients 18 years of age and older.

Risk-benefit assessment: The applicant established the safety and efficacy of their product for the proposed use and provided sufficient information to inform product labeling. The efficacy of the product justifies the risks, which include the potential for adrenal suppression and local skin reactions.

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) is not required.

Postmarketing requirements (PMR) and commitments (PMC):

Conduct a safety, pharmacokinetics, and hypothalamic-pituitary-adrenal (HPA) axis suppression study of Ultravate (halobetasol propionate) lotion, 0.05% under maximal use conditions in adolescents 12 years to 16 years 11 months of age with plaque psoriasis receiving two weeks of treatment. The applicant is required to conduct this study under the Pediatric Research Equity Act.

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/s/

JILL A LINDSTROM
11/06/2015