CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050803Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	July 15th, 2010
From	Susan J. Walker, M.D., F.A.A.D.
Subject	Division Director Summary Review
NDA #	NDA 050803
Applicant Name	Stiefel Laboratories, Inc.
Date of Submission	October 16th, 2009
PDUFA Goal Date	July 16th, 2010
Proprietary Name / Established (USAN) Name	Veltin/ clindamycin phosphate, tretinoin
Dosage Forms / Strength	Gel, 1.2%/0.025%
Proposed Indication	Topical treatment of acne vulgaris
Action	**Approval**

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Gary Chiang, M.D., M.P.H.
Statistical Review	Mathew Soukup, Ph.D.
Pharmacology Toxicology Review	Jill Merrill, Ph.D.
CMC Review/OBP Review	Shulin Ding, Ph.D.
Microbiology Review	Peter Coderre, Ph.D.
Clinical Pharmacology Review	Chinmay Shukla, Ph.D.
DDMAC	Andrew Haffer, Pharm.D., Shefali Doshi, M.D.
DSI	Ni Khin, M.D. (first cycle)
CDTL Review	David Kettl, M.D.
OSE/DMEPA	Zachary Oleszczuk, Pharm.D.
OSE/DRISK	Steve Morin, R.N., B.S.N.
Other	Steven Thomson, Tapash Ghosh, Ph.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This application is a Complete Response to the Agency original action of June 10th, 2005 and provides for the use of a topical gel, containing a combination of the two active ingredients clindamycin 1% and tretinoin 0.25%, for the treatment of acne vulgaris once daily in patients 12 years and older. The applicant has provided adequate information to demonstrate safety and efficacy of their product, and I concur with the recommendations of the review team for approval.

2. Background

Veltin Gel is a combination drug product composed of clindamycin, 1% and tretinoin, 0.025% in an aqueous topical gel base for the treatment of acne vulgaris. The active ingredients in this formulation are not novel, and have been well studied for the treatment of acne vulgaris with multiple prior approvals in various formulations. Clindamycin is classified as a bactericidal antibiotic belonging to the class of lincosamides with anti-inflammatory activity that is used to treat inflammatory lesions of acne. Clindamycin inhibits bacterial protein synthesis by irreversibly binding to the 50S subunit of the bacterial ribosome. Clindamycin phosphate is biologically inactive and is rapidly hydrolyzed to active clindamycin sulfoxide *in-vivo*. Tretinoin (all-trans retinoic acid) is a natural oxidative metabolite of vitamin A (retinol) and belongs to the class of retinoids. Low concentrations (4-14 nmol/L) are found normally in human circulation and bind to albumin. Tretinoin is a comedolytic agent and its effectiveness has been attributed to its ability to reduce follicular hyperkeratinization and inhibit inflammatory reactions.

An earlier formulation of the drug product, Velac Gel, (b) (4) was determined to have equivocal clastogenic activity in a non-clinical chromosome aberration study and, when tested in a 26-week non-clinical dermal carcinogenicity study in Tg.AC mice, the vehicle alone caused a statistically significant increased incidence of skin papillomas compared to the untreated controls. The drug product was reformulated (b) (4) and the applicant conducted an additional phase 3 trial (Study W0265-03) which included the combination drug product, each monad, and vehicle gel.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. The application contains sufficient information to assure the identity, strength, purity, and quality of the drug product. Manufacturing site inspections were determined to be acceptable on March 18th, 2010. Stability testing supports an expiry of 18 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Non-clinical studies of the original formulation resulted in conclusions that Velac Gel (OF) was determined to have equivocal clastogenic activity in a chromosome aberration study and when tested in a 26-week dermal carcinogenicity study in Tg.AC mice, the vehicle alone caused a statistically significant increased incidence of skin papillomas compared to the untreated controls. Clindamycin in the Velac Gel caused further significant dose related increases in papillomas relative to the vehicle controls and untreated animals. The applicant posited that these changes were a non-specific response to irritation but the Executive Carcinogenicity Assessment Committee (ECAC) did not concur. The sponsor subsequently reformulated the drug product. (b) (4) and (b) (4) (POE-4) (b) (4) in (b) (4). The reformulated product proposed for marketing contains the same concentration of active ingredients as found in the previous formulation, with the exception (b) (4) POE-4, is identical to the originally tested formulation.

The reformulated product was evaluated in a two year dermal carcinogenicity study designed to evaluate dermal proliferative changes following application of 1% clindamycin in new vehicle vs. new vehicle vs. sham control. No treatment related tumors were demonstrated and the test articles were considered to be non-tumorigenic.

The previously reviewed chronic toxicology, genetic toxicology, reproductive and developmental toxicology information stands in support of the proposed drug product. Clindamycin at the clinical concentration in the reformulated vehicle and the reformulated vehicle have been evaluated in a two year dermal carcinogenicity study with acceptable results, and clindamycin was evaluated in a 27 week dermal carcinogenicity study evaluating carcinogenic potential across a range of concentrations bracketing the concentration in Velac. The applicant has also relied upon literature (505 (b) (2)) to provide additional toxicology information to support the safety of clindamycin and tretinoin.

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

5. Clinical Pharmacology/Biopharmaceutics

Bioavailability was evaluated in a maximal use study in which systemic exposure of clindamycin, clindamycin sulfoxide (an active metabolite of clindamycin), and tretinoin were evaluated. The results demonstrated that the bioavailability of clindamycin and clindamycin sulfoxide in the original formulation (OF) appeared to be enhanced compared to the bioavailability in the reformulated vehicle (RF), however, it was determined that the non-clinical studies were sufficiently dosed to provide support for the formulation and there were no clinical safety concerns.

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

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

The applicant has provided adequate information to support the efficacy of the drug product and has completed a development program consistent with agency recommendations.
The original application included two phase three trials demonstrating the efficacy of the original formulation. However, preclinical testing (described above) led to safety concerns and the application was not approved. Preclinical outcomes provided in the original submission precluded use of the original formulation in further comparative clinical testing subsequent to the formulation change. Following discussion with the agency it was recommended that the applicant should provide an additional phase 3, four arm trial with the new formulation intended to demonstrate that safety and efficacy determinations were consistent with the outcomes in the phase 3 trials provided in the original application.

Studies with the original formulation (OF) include two phase 3 trials (VLC.C.304 and 305). Studies with the new formulation include phase 3 trial W0265-03 enrolling 1,656 subjects randomized to Veltin Gel (clindamycin/tretinoin), clindamycin gel, tretinoin gel, and vehicle. The agency evaluation of efficacy used the following criteria:

IGA: Success = week 12 score of 0 or 1 with at least a two grade improvement. The objective for assessing IGA success was to establish the superiority of Veltin Gel over each monad, clindamycin gel and tretinoin gel, and vehicle gel.
Lesion Counts: The absolute change from baseline to week 12 was observed. The objective for assessing lesion counts was to establish the superiority of Veltin Gel over clindamycin gel for total and non-inflammatory lesions, superiority of Veltin Gel over tretinoin gel for total and

inflammatory lesions, and superiority of Veltin Gel over vehicle gel for total, inflammatory, and non-inflammatory lesions.

In study W0265-03 the drug product was superior to each monad and vehicle for IGA success. IGA success in this protocol was defined as a two grade improvement in investigator's global assessment. While this evaluation has some utility, it does not provide information regarding the performance of the product related to "clearing" the subject's acne vulgaris. The agency evaluation of IGA success included a week 12 score of 0 or 1 and at least a two-grade improvement. The product was successful under both definitions. Veltin Gel was also superior to each monad and vehicle for treatment of total lesions and for treatment of inflammatory lesions. Veltin Gel was superior to tretinoin gel and vehicle, but was not superior to clindamycin. For non-inflammatory lesions, Veltin Gel was superior to clindamycin gel and vehicle but not to tretinoin gel.

Table 1: Efficacy Summary (ITT/LOCF); Study W0265-03

	Veltin Gel (N=476)	Clindamycin Gel (N=467)	Tretinoin Gel (N=464)	Vehicle Gel (N=242)
ISGA Success: 0 or 1 with a Two Grade Improvement				
Success (%)	158 (33.2)	112 (24.0)	105 (22.6)	43 (17.8)
p-value†	-	0.0018	< 0.001	< 0.001
Success: ISGA Two Grade Improvement				
Success (%)	173 (36.3)	124 (26.6)	121 (26.1)	49 (20.2)
p-value†		0.0015	< 0.001	< 0.001
Absolute Change Total Lesions				
Mean Change (SD)	38.7 (26.8)	34 (25.2)	36 (28.3)	28.1 (27.7)
p-value‡	-	0.0028	0.037	< 0.001
Absolute Change Inflammatory Lesions				
Mean Change (SD)	15.5 (10.3)	14.5 (9.4)	13.9 (11.1)	11.1 (11.7)
p-value‡	-	0.1797	0.0022	< 0.001
Absolute Change Non-Inflammatory Lesions				
Mean Change (SD)	23.2 (20.4)	19.5 (19.7)	22.1 (21.7)	17.0 (20.6)
p-value‡	-	0.001	0.2541	< 0.001

†CMH stratified by 'analysis center' (Source: Biostatistical reviewer's analysis)
‡p-value is based on an ANCOVA models with terms for treatment and 'analysis center' with covariate for the baseline lesion count (Source: Biostatistical reviewer's analysis)
Source of table: Statistical Review and Evaluation by Mat Soukup, Ph.D.

Analyses were conducted to assess the consistency of findings across all studies, comparing the efficacy of the reformulated product with that of the original formulation studied. While there are limitations to this methodology, in this case, the agency and the sponsor reached prior agreements on a path forward for the product in light of the non-clinical study outcomes and considering the clinical testing performed during the development program. I concur that the studies conducted demonstrate consistent outcomes.

Table 2: Investigator Global Results (ITT/LOCF); ISE

	Combination Gel	Clindamycin Gel	Tretinoin Gel	Vehicle Gel
Study VLC.C.304				
X/N (%)	72/309 (23.3)	43/311 (13.8) 9.4	36/310 (11.6)	12/153 (7.8)
Trt. Effect (ˆδ)		(3.3, 15.5)	11.6	15.1
95% CI for ˆδ			(5.7, 17.5)	(8.7, 21.5)
Study VLC.C.305				
X/N (%)	95/325 (29.2)	81/324 (25.0)	79/325 (24.3)	18/162
Trt. Effect (ˆδ)		4.2	4.9	(11.1) 17.8
95% CI for ˆδ		(-2.6, 11)	(-1.9, 11.7)	(10.8, 24.7)
Study W0265-03				
X/N (%)	158/476 (33.2)	112/467 (24.0)	105/464 (22.6)	43/242
Trt. Effect (ˆδ)		9.2	10.5	(17.8) 15.2
95% CI for ˆδ		(3.4, 14.9)	(4.8, 16.2)	(8.8, 21.6)

Source: Agency Biostatistics reviewer analysis: Statistical Review and Evaluation by Mat Soukup, Ph.D. Table 17
Note: Confidence intervals are unadjusted and based upon Wilson estimates of the percent of success

Table 3: Absolute Change in Total Lesions (ITT/LOCF); ISE

	Combo Vs. Clindamycin	Combo Vs. Tretinoin	Combo Vs. Vehicle
Study VLC.C.304			
β_3	11.1	9.2	21.8
95% CI for β_3	(7.0, 15.3)	(5.2, 13.3)	(16.2, 27.4)
Study VLC.C.305			
β_3	7.5	4.7	21.9
95% CI for β_3	(3.7, 11.2)	(1.1, 8.3)	(16.8, 27.1)
Study W0265-03			
β_3	4.1	2.8	11.8
95% CI for β_3	(1.5, 6.7)	(0.0, 5.6)	(8.4, 15.2)

Source: Biostatistical Reviewer's Analysis. Estimates and confidence intervals based on model.

Table 4: Absolute Change in Inflammatory Lesions (ITT/LOCF); ISE

	Combo Vs. Clindamycin	Combo Vs. Tretinoin	Combo Vs. Vehicle
Study VLC.C.304 β_3 95% CI for β_3	1.8 (0.3, 3.3)	3.5 (2.1, 5)	6.4 (4.5, 8.3)
Study VLC.C.305 β_3 95% CI for β_3	1.8 (0.3, 3.3)	2.1 (0.7, 3.5)	6.0 (4.0, 8.1)
Study W0265-03 β_3 95% CI for β_3	0.7 (-0.3, 1.8)	1.7 (0.6, 2.9)	4.5 (3.1, 6.0)

Source: Biostatistical Reviewer's Analysis . Estimates and confidence intervals based on model.

Table 5: Absolute Change in Non-Inflammatory Lesions (ITT/LOCF); ISE

	Combo Vs. Clindamycin	Combo Vs. Tretinoin	Combo Vs. Vehicle
Study VLC.C.304 β_3 95% CI for β_3	9.3 (6.0, 12.6)	5.7 (2.5, 8.9)	15.4 (10.8, 19.9)
Study VLC.C.305 β_3 95% CI for β_3	5.6 (2.7, 8.4)	2.5 (-0.1, 5.2)	15.9 (11.9, 19.9)
Study W0265-03 β_3 95% CI for β_3	3.4 (1.4, 5.3)	1.1 (-0.9, 3.1)	7.4 (4.9, 9.8)

Source: Biostatistical Reviewer's Analysis. Estimates and confidence intervals based on model.

8. Safety

The safety profiles of both clindamycin and tretinoin are well established and no new safety concerns are raised by this application.

Across studies the majority of subject discontinuations were attributed to application site reactions, which are an anticipated adverse event with these topical active ingredients. The most frequently reported events were dermatitis, dryness, erythema, exfoliation and irritation. No subject experienced colitis or other abdominal symptoms of antibiotic associated colitis. No serious adverse events were associated with Veltin Gel and no deaths occurred.

Table 1: Treatment-Related Adverse Reactions Reported by ≥1% of Subjects

	VELTIN Gel N=1104 n (%)	**Clindamycin Gel N=1091 n (%)**	**Tretinoin Gel N=1084 n (%)**	**Vehicle Gel N=552 n (%)**
Patients with at least one adverse reaction	140 (13)	38 (3)	141 (13)	17 (3)
Application site dryness	64 (6)	12 (1)	62 (6)	3 (1)
Application site irritation	50 (5)	4 (<1)	57 (5)	5 (1)
Application site exfoliation	50 (5)	2 (<1)	56 (5)	2 (<1)
Application site erythema	40 (4)	6 (1)	39 (4)	3 (1)
Application site pruritus	26 (2)	7 (1)	23 (2)	6 (1)
Sunburn	11 (1)	6 (1)	7 (1)	3 (1)
Application site dermatitis	6 (1)	0 (0)	8 (1)	1 (<1)

Local skin reactions actively assessed at baseline and end of treatment with a score > 0 are presented in Table 2.

Table 7: VELTIN GEL-Treated Patients with Local Skin Reactions

	VELTIN GEL		VEHICLE GEL	
Local Reaction	Baseline N= 476 N (%)	End of Treatment N= 409 N (%)	Baseline N= 219 N (%)	End of Treatment N= 209 N (%)
Erythema	24%	21%	31%	35%
Scaling	8%	19%	14%	12%
Dryness	11%	22%	18%	13%
Burning	8%	13%	8%	4%
Itching	17%	15%	22%	14%

Colitis has very rarely been reported in association with use of topical clindamycin. The labeling for Veltin Gel will be consistent with other topical clindamycin products.

I concur with the primary clinical reviewer and cross-discipline team leader that the applicant has provided adequate evidence to establish the safety of the proposed drug product for the treatment of acne vulgaris.

9. Advisory Committee Meeting

No advisory committee meeting was held for this application.

10. Pediatrics

PeRC has found that the product does not trigger PREA and does not require review prior to approval.

11. Unresolved Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

There are no unresolved issues.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - This application will be approved.

- Risk Benefit Assessment – There are no unresolved issues and the product presents no new or novel elements related to either risk or benefit. The safety and efficacy profile of the active ingredients is well understood and this product raises no concerns.

- Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies- Risk evaluation and mitigation strategies beyond standard labeling are neither necessary nor envisioned for this product.

- Recommendation for other Postmarketing Requirements and Commitments - None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50803	ORIG-1	STIEFEL A GSK CO	Veltin

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/s/

SUSAN J WALKER
07/16/2010