

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**050803Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	June 25, 2010
<b>From</b>	David Kettl, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	50-803
<b>Supplement#</b>	000      Related IND: 65,369 (b) (4)
<b>Applicant</b>	Stiefel, a GSK Company
<b>Date of Submission</b>	October 16, 2009
<b>PDUFA Goal Date</b>	July 16, 2010
<b>Proprietary Name / Established (USAN) names</b>	Veltin Gel (clindamycin 1% and tretinoin 0.025%)
<b>Dosage forms / Strength</b>	Topical Gel
<b>Proposed Indication(s)</b>	Treatment of Acne vulgaris
<b>Recommended:</b>	<i>Approval</i>

### 1. Introduction

This 505(b)(2) application for a new formulation of clindamycin 1% and tretinoin 0.025% is from Stiefel, a GSK company, and is submitted for the topical treatment of acne vulgaris. The current submission is a Complete Response to the June, 2005 Non-Approvable Letter issued (b) (4).

Since the sponsor has relied on literature data to provide pivotal toxicology information to support the safety of clindamycin and tretinoin (for fertility and peri-/postnatal development information for clindamycin and tretinoin and for tretinoin carcinogenicity information), this NDA is a 505(b)(2) regulatory submission.

The original NDA for this product, using the originally proposed trade name of Velac Gel (clindamycin 1% and tretinoin 0.025%), was submitted on August 23, 2004 by Connetics Corporation under (b) (4). A “Not Approvable” action letter was issued by the Agency on June 10, 2005 due to a positive carcinogenicity signal observed in a Tg.AC mouse assay after dermal exposure in both the vehicle and clindamycin phosphate arms. The review team concluded that efficacy had been adequately demonstrated, but deemed that safety had not been established due to the carcinogenicity potential of the vehicle.

(b) (4) the applicant reformulated Velac Gel to contain only excipients found in the US FDA’s Inactive Ingredients Guide (IIG). Specifically, (b) (4), polyoxyethylene 4 monolauryl ether (POE 4) was (b) (4) in the vehicle.

The proposed proprietary name for the new formulation, (b) (4) is Veltin Gel (clindamycin 1% and tretinoin 0.025%). This reformulated topical gel product is the subject of the current application.

Following discussions with the Agency at a post-special protocol assessment guidance meeting on December 18, 2007, the sponsor was asked to perform 6 clinical studies using the reformulated combination gel product in order to establish a clinical bridge between the new formulation of Veltin Gel and the previous formulation of Velac Gel. Specifically, studies conducted with Veltin Gel include a phase 1 cutaneous irritation study (CTG.103), a phase 1 phototoxicity study (W0265-103), a phase 1 photoallergy study (W0265-104), a phase 2 bioavailability study (W0265-02), a phase 3b tolerability study with benzoyl peroxide (W0265-306), and a phase 3 safety and efficacy study (W0265-03).

These studies provide an adequate demonstration of safety and efficacy for the reformulated Veltin Gel, and the applicant has provided sufficient nonclinical information to assure that the concerns regarding potential carcinogenicity of the final, to be marketed product have been adequately addressed.

No new safety concerns were identified in the clinical trials performed with Veltin Gel as compared to previously approved formulations of topical tretinoin, topical clindamycin phosphate or in combination.

The clinical review recommends an approval action for this application, with which this CDTL review concurs, pending successful conclusion of pending labeling negotiations with the applicant.

There are no outstanding issues from the CMC, Pharmacology/Toxicology and Biostatistics reviews.

## **2. Background**

Clindamycin and tretinoin are approved topical agents in the treatment of acne vulgaris. Topical clindamycin phosphate 1% was first approved in 1980 and topical tretinoin 0.025% in 1975. Tretinoin has since been marketed for a variety of dermatoses at strengths ranging from 0.025% to 0.1% topical formulations. Both clindamycin and tretinoin are also available for systemic use.

The original IND submission for this application was submitted October 10, 2002. The original NDA was submitted on August 23, 2004.

Study AA81EW.7D8T.BTL: 26-Week Dermal Carcinogenicity Study in Tg.AC Mice, concluded there was statistically significant higher tumor incidence, for both genders, in each of the four dose groups compared to the untreated group. These results were reviewed by the Executive Carcinogenicity Assessment Committee (ECAC) on March 29, 2005, which concluded:

The Committee noted that positive results in the Tg.AC assay indicate that a substance may be either a promoter or a complete carcinogen and concurred that the vehicle of Velac gel alone caused a statistically significant increased incidence of skin papillomas compared to the untreated controls and that clindamycin in Velac gel caused further significant dose-related increases in papillomas relative to the vehicle controls and untreated animals.

This assessment was the basis of the June 10, 2005 non-approval action, as the potential risk outweighed the demonstration of efficacy in the two phase 3 trials.

The applicant was required to submit full carcinogenicity data for the reformulated product prior to approval. Over the course of several meetings with the Agency and a Special Protocol Review, the applicant determined that a protocol using the original formulation was not possible due to the concerns regarding possible carcinogenicity. A four arm phase 3 trial which would demonstrate superiority to vehicle as well as comparison to the clindamycin and tretinoin monads was judged acceptable to determine safety and efficacy of the reformulated Veltin Gel in addition to providing adequate carcinogenicity data.

The applicant successfully completed the requirements agreed to following the 2005 non-approval action and has provided adequate information to provide an acceptable risk benefit basis on which to approve the current Veltin formulation for the treatment of acne vulgaris.

### **3. CMC/Device**

The proposed product, Veltin gel, is a yellowish, opaque, aqueous gel containing two commercially available, USP grade active pharmaceutical ingredients: clindamycin phosphate (1.2% equivalent to 1% of clindamycin) and tretinoin (0.025%). Both clindamycin phosphate and tretinoin are fully solubilized in the formulation.

The sponsor purports that the combination of clindamycin and tretinoin in Veltin Gel potentially offers comedolytic, anti-bacterial, and anti-inflammatory pharmacological properties that are effective in the treatment of acne.

The drug product is supplied in 30 g aluminum tubes. (b) (4)



The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP.

The applicant provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product

quality of the drug substance and drug product. The NDA also has provided sufficient stability information for the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

The CMC review also affirms that the proposed to-be marketed formulation is the same formulation used in the Phase 3 clinical study. It is also the same formulation used in the bioavailability study, and the registration stability studies.

The CMC review by Dr. Shulin Ding recommends approval for this application, pending successful completion of labeling negotiations. Carton and container labeling has been agreed to upon CMC review.

No outstanding CMC issues remain that would impact on an approval action for this application.

## 4. Nonclinical Pharmacology/Toxicology

The applicant conducted sub-chronic toxicity tests in both a rodent and non-rodent model on the previous formulation, Velac Gel (1% clindamycin, 0.025% tretinoin), which was reviewed in the original NDA application.

Velac Gel was determined to be non-mutagenic in an *in vitro* Ames *Salmonella* reversion test and was tested without effect in a limit teratology test in rodents. However, Velac Gel was determined to have equivocal clastogenic activity in a chromosome aberration assay 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 vehicle caused further significant dose-related increases in papillomas relative to the vehicle controls and untreated animals. These non-clinical findings formed the basis for the action letter (June 10, 2005) in which the drug was not approved.

The applicant reformulated the original gel by [REDACTED] (b) (4)

[REDACTED] polyoxyethylene 4 monolauryl ether (POE 4) [REDACTED] (b) (4)

[REDACTED] The new formulation was renamed Veltin Gel to distinguish the new product from the former Velac Gel formulation. The reformulated Veltin Gel, (clindamycin 1% - tretinoin 0.025%) contains the same concentration of active ingredients as found in the previous Velac formulation and, with the [REDACTED] (b) (4) POE 4, is identical to the original Velac Gel.

The nonclinical deficiencies noted in the action letter, specifically the positive carcinogenicity signal in the Tg.AC mouse dermal carcinogenicity model, have been addressed by

reformulation. Clindamycin at the clinical concentration (1%) in the reformulated vehicle has been tested in a 2-year dermal carcinogenicity study (NPB00012; reviewed within) with adequate results. Consistent with the Agency's guidance, the sponsor obtained the right of reference to a 27-week dermal carcinogenicity study of clindamycin phosphate (0, 0.5, 1, and 2 %) in a different gel-formulation to provide evidence that clindamycin does not display carcinogenic potential across a range of concentrations bracketing the clinical concentration of the CT Gel product.

Although the study did not indicate a carcinogenic concern for clindamycin, technical inadequacies precluded further evaluation of this study and the results will not appear in the label.

The sponsor was previously informed that literature information describing both the carcinogenic potential of tretinoin and the limitations of this information could appear in the drug product label (IND 65,369, 2-6-03).

No reproductive and developmental toxicology studies were included in this NDA submission. Labeling recommendations for these sections are based on literature references, and mirror labeling for related acne topical products containing clindamycin and tretinoin. On this basis, the application has been deemed a 505 (b)(2) application.

The nonclinical team determined that the current application is approvable from a pharmacological/toxicological perspective, and no additional nonclinical studies are recommended. There are no outstanding nonclinical issues.

Recommended labeling revisions to Sections 8, Pregnancy, 12, Clinical Pharmacology, and 13, Nonclinical Toxicology, have been incorporated in the revised prescribing information sent to the sponsor. Final agreed upon labeling is pending as of the date of this CDTL review.

## **5. Clinical Pharmacology/Biopharmaceutics**

The bioavailability study (W0265-02) was designed to evaluate the systemic exposure of clindamycin, clindamycin sulfoxide (active metabolite of clindamycin) and tretinoin, individually, following multiple topical applications of either Veltin Gel or Velac Gel. The study consisted of a 5-day treatment period during which subjects with acne were instructed to apply 3 grams of the study product (Veltin Gel or Velac Gel) once daily (every morning) to the face, neck, upper chest and upper back. The specific aim of this study was to show that the levels of absorption of Veltin Gel were similar to those with Velac Gel.

The exposure of clindamycin and clindamycin sulfoxide was increased about two times while the exposure of tretinoin was comparable with the original Velac Gel formulation. However, no events suggestive of systemic toxicity were reported by any subjects in this study or in the Phase 3 (W0265-03) safety and efficacy study. The non-clinical studies were dosed at sufficient levels to allow for the increase in bioavailability of clindamycin and clindamycin sulfoxide.

Despite the theoretical concern that the higher clindamycin exposure would present a safety concern, no clinical or nonclinical event was judged to be related to the increased exposure. The Biopharmaceutics review, by Dr. Chinmay Shukla, concludes that an increase in clindamycin and clindamycin sulfoxide exposure with Veltin Gel might not result in clinically meaningful safety concerns above the referenced treatment. The clinical team concurs with this assessment given the low levels of bioavailability.

No studies to address pharmacodynamic drug interactions were included in this submission. Drug-drug interactions are not normally evaluated for topically applied products because of low plasma exposure and they were not studied for this application. Similarly, no clinical studies were conducted to evaluate the effects of renal or hepatic impairment on the pharmacokinetics of Veltin Gel.

The Biopharmaceutics review conclusion was that the studies conducted for the development of Veltin Gel were adequate from a clinical pharmacology perspective.

## 6. Clinical Microbiology

No microbiology data were submitted with this application, and no antimicrobial claims are requested by the applicant. The clinical microbiology reviewer, Dr. Peter Coderre, recommends that the application is approvable from his perspective.

The Clinical Microbiology review, however, outlines concerns regarding the impact of clindamycin use on the development of bacterial resistance, which would impact the utility of subsequent clindamycin treatment for patients who might require it for a serious infection.

The Microbiology review recommends placement of this information in the Warnings and Precautions section of the Veltin label. The long term goal of the Division of Anti-Infective and Ophthalmology Products is to add similar warnings to the entire class of clindamycin products which includes oral and parenteral formulations as well as topical products such as the product that is the subject of the current application.

Labeling for inducible clindamycin resistance has not yet been requested of any other approved clindamycin product to date. Since the exposure to parenteral and oral products is much greater than levels seen in topical acne products, the clinical review team recommends noting the association with antimicrobial resistance to *P. acnes* in the current Veltin label, but awaits consistent language to be incorporated into systemic clindamycin products before listing this as a Warning in topical clindamycin labeling. Once the specific language for oral and parenteral clindamycin product labeling is agreed upon, the entire class of topical clindamycin acne products, which would include Veltin upon approval of this application, could be updated with labeling supplements at the same time for consistency across the indication.

The recommended labeling for Section 12.4 is listed below:

## **12.4 Microbiology**

No microbiology studies were conducted in the clinical trials with this product.

### *Mechanism of Action*

Clindamycin binds to the 50S ribosomal subunit of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing protein synthesis. Clindamycin has been shown to have *in vitro* activity against *Propionibacterium acnes* (*P. acnes*), an organism that has been associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical studies with VELTIN Gel. *P. acnes* resistance to clindamycin has been documented.

### *Inducible Clindamycin Resistance*

The treatment of acne with antimicrobials is associated with the development of antimicrobial resistance in *P. acnes* as well as other bacteria (e.g. *Staphylococcus aureus*, *Streptococcus pyogenes*). The use of clindamycin may result in developing inducible resistance in these organisms. This resistance is not detected by routine susceptibility testing.

### *Cross Resistance*

Resistance to clindamycin is often associated with resistance to erythromycin.

This proposed labeling is somewhat different from that recommended by the Clinical Microbiology review, but the clinical team feels this is adequate given the expected clinical use of this product in an essentially healthy population, in conjunction with the post marketing experience of other clindamycin products.

## **7. Clinical/Statistical- Efficacy**

The Agency issued a non-approval action on June 10, 2005 for Velac Gel, as the potential risk of the potentially carcinogenic excipient in the vehicle formulation outweighed the statistical demonstration of efficacy in the two phase 3 trials for the originally submitted Velac Gel.

Several meetings were held with the applicant (or predecessor applicants) after the non-approval action. On October 3, 2005, a Special Protocol Assessment (SPA) for a phase 3 study with the newly reformulated product was submitted to IND 65,369 for Agency review. The typical recommendation for a bridging study with old and new formulations was deemed ethically problematic given the positive mouse carcinogenicity assay. While a small study was conducted to assess the relative bioavailability of the original Velac and reformulated Veltin Gel products, the Agency concurred that a large bridging study exposing subjects to a potentially carcinogenic product should not be conducted, and a single phase 3, four arm trial was recommended provided that efficacy and safety determinations were consistent with the findings of the original application.

This current submission is a Complete Response to the Not-Approvable Letter issued (b) (4). Included in this submission were the following studies conducted with the reformulated Veltin Gel: a phase 1 cutaneous irritation study (CTG.103), a phase 1 phototoxicity study (W0265-103), a phase 1 photoallergy study (W0265-104), a phase 2 bioavailability study (W0265-02), a phase 3b tolerability study with benzoyl peroxide (W0265-306), and a phase 3 safety and efficacy study (W0265-03). The phase 3 safety and efficacy study was the focus of the current clinical and biostatistics reviews.

The single phase 3 trial, Study W0265-03, was conducted with the reformulated Veltin Gel product with the objective of establishing the safety and efficacy of Veltin Gel over each monad and vehicle. This phase 3 trial enrolled 1,656 subjects randomized to Veltin Gel, clindamycin gel, tretinoin gel, or vehicle gel.

Efficacy is supported by the two previously submitted phase 3 trials (VLC.C.304 & VLC.C.305) with the original formulation of Velac Gel, which differs from the to be marketed Veltin Gel (b) (4).

In the SPA review of the Phase 3 protocol for Study W0265-03, the Agency stated that if the efficacy results of Veltin Gel were similar to efficacy results observed in Studies VLC.C.304 and VLC.C.305 conducted with the original formulation, this would be sufficient to support a determination of efficacy for the new Veltin formulation. A detailed review of studies VLC.C.304 and VLC.C.305 was conducted during the first cycle for (b) (4) in the Agency statistical review dated 4/26/2005.

The evaluation of co-primary endpoints is the proportion of subjects who had a minimum 2-grade improvement in the ISGA score from baseline from baseline to week 12 (end of study) and the absolute change in lesion counts (total, inflammatory, non-inflammatory) from baseline to week 12.

The Agency biostatistics review used the following criteria for assessments of efficacy:

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. 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, Veltin Gel was superior to each monad and vehicle for IGA success. Veltin Gel was also superior to each monad and vehicle for total lesions. For inflammatory lesions, Veltin Gel was superior to Tretinoin Gel and vehicle, but not superior to Clindamycin Gel. For non-inflammatory lesions, Veltin Gel was superior to Clindamycin Gel and vehicle, but not for Tretinoin Gel (Table 24). Thus, Study W0265-03 met all efficacy objectives.

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

	<b>Veltin Gel (N=476)</b>	<b>Clindamycin Gel (N=467)</b>	<b>Tretinoin Gel (N=464)</b>	<b>Vehicle Gel (N=242)</b>
<b>ISGA Success: 0 or 1 with a Two Grade Improvement</b>				
Success (%)	158 (33.2)	112 (24.0)	105 (22.6)	43 (17.8)
p-value†	-	0.0018	< 0.001	< 0.001
<b>Success: ISGA Two Grade Improvement</b>				
Success (%)	173 (36.3)	124 (26.6)	121 (26.1)	49 (20.2)
p-value†	-	0.0015	< 0.001	< 0.001
<b>Absolute Change Total Lesions</b>				
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
<b>Absolute Change Inflammatory Lesions</b>				
Mean Change (SD)	15.5 (10.3)	14.5 (9.4)	13.9 (11.1)	11.1 (11.7)
p-value‡	-	.01797	0.0022	< 0.001
<b>Absolute Change Non-Inflammatory Lesions</b>				
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: Agency 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: Agency Statistical Review and Evaluation by Mat Soukup, Ph.D.

Secondary endpoints were included in the protocol (percent change of lesion counts and IGA; and subject assessments), but no secondary endpoints have been proposed by the applicant to be included in product labeling. As such, no further analyses were conducted on secondary clinical endpoints assessed during the clinical trial.

To assess the consistency of efficacy findings across all phase 3 trials, analyses were conducted by the biostatistics team to compare the efficacy of the reformulated Veltin product with that of original Velac formulation that was the subject of two large phase 3 trials that were submitted in the original NDA application. Treatment effects for the IGA endpoint were similar in Study VLC.C.304 and W0265-03 which were higher than in Study VLC.C.305. For assessing changes in lesion counts, the treatment effects in Study W0265-03 were smaller than in both Studies VLC.C.304 and VLC.C.305. Overall, efficacy trends of all co-primary endpoints were consistent across all phase 3 trials.

The sponsor did not provide a formal statistical analysis plan for comparing efficacy data from all phase 3 trials nor was the efficacy data presented integrating data from all phase 3 trials. The biostatistics reviewer, Dr. Soukup, conducted an Agency review of efficacy results across the three phase 3 trials, using the current definition for success in IGA scores (the percent of subjects with a week 12 IGA score of 0 or 1 with at least a two grade improvement) which was not used in the original Agency Velac study analyses.

Overall, the trends in treatment effects were consistent across each of the three studies in which the smallest treatment effect occurred when comparing Veltin Gel to Clindamycin Gel. The largest treatment effect was observed when comparing Veltin Gel to Vehicle Gel.

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

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

Similar consistency in results across the trials was demonstrated for lesion count endpoints as illustrated by Dr. Soukup in Table 3:

**Table 3: Absolute Change in Total Lesions (ITT/LOCF); All Trials**

	Combo Vs. Clindamycin	Combo Vs. Tretinoin	Combo Vs. Vehicle
<b>Study VLC.C.304</b>			
$\hat{\beta}_3$	11.1	9.2	21.8
95% CI for $\hat{\beta}_3$	(7.0, 15.3)	(5.2, 13.3)	(16.2, 27.4)
<b>Study VLC.C.305</b>			
$\hat{\beta}_3$	7.5	4.7	21.9
95% CI for $\hat{\beta}_3$	(3.7, 11.2)	(1.1, 8.3)	(16.8, 27.1)
<b>Study W0265-03</b>			
$\hat{\beta}_3$	4.1	2.8	11.8
95% CI for $\hat{\beta}_3$	(1.5, 6.7)	(0.0, 5.6)	(8.4, 15.2)

The primary clinical and biostatistics reviewers have concluded that statistical superiority of the combination drug product Veltin Gel has been adequately demonstrated in one well-controlled, phase 3, multi-center, randomized, double-blind, vehicle-controlled, 12 week clinical trial (W0265-03). In addition, superiority of the combination to its monads was demonstrated in two previously conducted phase 3 clinical trials with the previously submitted Velac Gel formulation. The results of these three clinical trials are consistent and support the conclusion that Veltin Gel applied once daily for 12 weeks is effective in the treatment of lesions of acne vulgaris.

While the two supportive trials conducted with Velac Gel are not the same, to-be-marketed formulation, they will be descriptively included in the Veltin Gel prescribing information.

The CDTL review concurs with this conclusion that efficacy has been adequately demonstrated and concurs that the development program was conducted in accordance with the Agency's recommendations.

## 8. Safety

The safety database for Veltin Gel clinical development program included 6 studies conducted with the newly reformulated drug product (CTG.103, W0265-103, W0265-104, W0265-02, W0265-306, and W0265-03). The pivotal phase 3 trial, W0265-03, enrolled 1,649 subjects.

476 subjects were exposed to Veltin Gel, 467 subjects to clindamycin gel, 464 subjects to tretinoin gel, and 242 subject to the vehicle gel.

No deaths occurred in the development program. Six subjects experienced serious adverse events. Only one of these occurred on Veltin Gel treatment. The case in the Veltin Gel arm involved a case of infectious mononucleosis requiring hospitalization for rehydration. None of the serious AE's was judged related to the use of the study product, and none resulted in discontinuation of the study product.

In the phase 3 trial (W0265-03), 14 subjects (7 in the Veltin Gel group and 7 in the tretinoin gel group) discontinued study product because of AEs. Almost all subjects that discontinued the study product due to adverse events were related to application site reactions. The most frequently reported events were dermatitis, dryness, erythema, exfoliation, and irritation. Events that resulted in study product discontinuation are similar between the Veltin Gel and tretinoin group, and were not unexpected given the experience of marketed topical products containing tretinoin.

No subject experienced colitis or other abdominal symptoms of antibiotic associated colitis. During the review of Velac Gel, one severe adverse event in trial VLC.C.304 (subject number 105-3034 - clindamycin arm) was noted. A 25 year old female was hospitalized for severe gastroenteritis 40 days after initiating treatment with clindamycin gel and experienced nausea, vomiting, and diarrhea. No action was taken with study drug. No cultures for *C. difficile* were obtained. Ova and parasites were negative and stool cultures were unremarkable. A specific diagnosis did not appear to be made beyond "viral" gastroenteritis. The subject recovered and completed the study on clindamycin.

A literature review identified several reports of antibiotic associated colitis associated with the use of topical clindamycin. Despite the absence of this rare adverse event in the clinical development for Veltin, labeling similar to existing clindamycin products is recommended for this potential serious adverse event.

Five local skin reactions: erythema, dryness, scaling, burning, and itching were actively assessed at each visit with scores of 0 to 5. Changes from baseline were minimal for the local tolerability assessments in the clindamycin gel and vehicle gel groups. For the Veltin Gel and tretinoin gel groups, the peak local tolerability assessments were most notable at week 2 and then decreased during weeks 4, 8, and 12. Veltin Gel was associated with less burning and itching at week 2 than tretinoin. A table for local reactions will be included in the Veltin Gel label, which is similar to the information for local reactions in the Ziana label.

No serum laboratory testing or ECG assessments were included in clinical trial W0265-03.

The recommended dermal safety studies were conducted with the reformulated Veltin Gel with the exception of the contact sensitization study study. The applicant requested a waiver with the assertion that the new formulation did not include any new excipient that would have any likely impact on a sensitization reaction. The review team concurred and waived the contact sensitization study requirement for Veltin Gel.

The review of the original submission for Velac, which included two large phase 3 trials, concluded, “Velac gel was shown to be safe in the 12 week clinical studies as conducted for this NDA, the adverse effects seen in patients were predominantly local and limited to application site and appeared to be in keeping with the known adverse effect profile of Tretinoin.” The determination that the product could not be approved was based solely on the results of the non-clinical carcinogenicity results that showed the vehicle of Velac gel to be a potential carcinogen.

No new safety concerns were identified in the clinical trials performed with Veltin Gel as compared to previously approved formulations of topical tretinoin, topical clindamycin phosphate or the products in combination. This CDTL review concurs with the primary clinical review by Dr. Chiang that the safety database is adequate to determine the safety of Veltin Gel for the treatment of acne vulgaris.

## **9. Advisory Committee Meeting**

No Advisory Committee meetings were held for this application.

## **10. Pediatrics**

The applicant requested a partial waiver for pediatric patients younger than 12 years old. The Pediatric Review Committee met on February 24, 2010, to review the application and age indication for Veltin Gel. Due to Veltin Gel’s pharmacoequivalence to Ziana Gel (approved in 2006, after the initial Velac action, but prior to this submission), and the fact that the original NDA application for the Velac formulation was submitted in 2004, the committee determined that this application for Veltin Gel did not trigger PREA requirements. Issuance of a waiver for patients under 12 was not required.

No further assessments for pediatric subjects are recommended as a condition of approval or post-approval requirement. The proposed age indication is in line with recent approvals of topical acne products.

## **11. Other Relevant Regulatory Issues**

DSI consultation for inspection of clinical study sites was deemed unnecessary following preliminary review of the phase 3 safety and efficacy data.

There were no issues with financial disclosures or GCP guidelines.

Clearance from the OND 505(b)(2) committee has been obtained.

There are no outstanding regulatory issues that would impact approval of this application.

## 12. Labeling

Review of the proposed label submitted by the applicant was based on evaluation of the clinical study for the NDA as well as DMEPA, DRISK, and DDMAC consultative reviews.

The only significant area of disagreement regarding the prescribing information relates to the information describing inducible clindamycin resistance in section 12.4. As described above in section 6 of this CDTL review, the complete recommendation of the Clinical Microbiology reviewer has not been included in proposed labeling in favor of noting the possibility of inducing resistance. The review team concluded that DDDP should await labeling which will be approved for oral and parenteral clindamycin products prior to labeling decisions for the class of topical clindamycin products approved for acne vulgaris.

The proposed name, Veltin Gel, has been accepted by DMEPA. Carton and container labeling has been accepted by the CMC reviewer and clinical team. DRISK has provided comments for the patient information section of the label which has been incorporated into the proposed labeling which is now with the applicant for concurrence. The principle area of disagreement with this section relates to the DMEPA suggestion (b) (4) (b) (4) which was not accepted by the review team which judged this (b) (4) to be promotional in nature.

Final labeling negotiations are in process with the applicant as of the date of this review.

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The clinical team leader concurs with the primary clinical reviewer that this product should be approved for the indication of acne vulgaris pending successful completion of labeling negotiations with the applicant.

- Risk Benefit Assessment

The efficacy for the indication of acne vulgaris has been adequately demonstrated. The results of the single trial conducted with the reformulated, to-be-marketed Veltin are consistent with, and supported by, two previous phase 3 trials with the Velac formulation, which differs only in (b) (4).

The safety findings are largely limited to local adverse events, with no serious adverse events deemed related to the study product. The local adverse events are expected with the two products contained in Veltin, and are similar in scope and severity to the post marketing experience of similar products approved for acne vulgaris.

The increased bioavailability of clindamycin and related clindamycin sulfoxide does not appear to be related to any adverse events, and the conclusion of the Clinical and Biopharmaceutics review teams is that the increased levels of clindamycin will have little clinical importance and does not require amplification in product labeling.

The benefits of this product outweigh the risks when used as the prescribing information recommends, and this CDTL review concurs that this application should be approved. The conclusion that this application should be approved is shared by each review discipline, and there are no outstanding approvability issues beyond agreement on final product labeling.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

REMS is not required nor recommended for this product. Labeling is adequate to inform prescribers and patients of expected risks and adverse events.

- Recommendation for other Postmarketing Requirements and Commitments

No recommendations for post-marketing requirements or commitments are suggested for this application.

- Recommended Comments to Applicant

There are no recommended comments exclusive of agreed upon labeling in PLR format. Labeling discussions are ongoing with the sponsor as of the date of this review, but there are only minor differences to be resolved at this time.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-50803

-----  
ORIG-1

-----  
STIEFEL A GSK CO Veltin

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

/s/  
-----

DAVID L KETTL

06/25/2010