

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
050803Orig1s000

MICROBIOLOGY REVIEW(S)

**Division of Anti-Infective and Ophthalmology Products
Consultation for HFD-540**

Clindamycin/Tretinoin
Connetics Corp.
NDA 50-803 SN043

Clinical Microbiology Review #1
Peter Coderre, PhD
10 May 2010

APPLICANT:

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SUBMISSION REVIEWED: NDA 50-803 SN043

INDICATION: Topical treatment of acne vulgaris in patients 12 years or older.

PRODUCT NAMES:

Proprietary name: VELTIN GEL
Compendia name: Clindamycin Phosphate, USP
Compendia name: Tretinoin, USP

CHEMICAL NAMES:

Clindamycin: Methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl- trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thi-L-threo-D-galacto-octopyranoside 2-(dihydrogen phosphate)
Tretinoin: trans 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-non-atetraenoic acid.

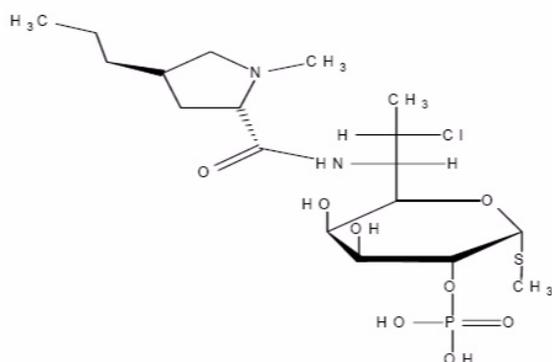
STRUCTURAL FORMULAE:

Clindamycin Phosphate

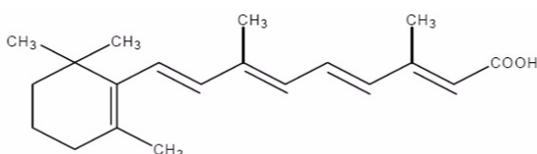
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Tretinoin



MOLECULAR FORMULAE:

Clindamycin Phosphate: $C_{18}H_{34}ClN_2O_8PS$ MW: 504.97
Tretinoin: $C_{20}H_{28}O_2$ MW: 300.40

PROPOSED DOSAGE FORM, DOSAGE, STRENGTH, ROUTE OF ADMINISTRATION, AND DURATION OF TREATMENT:

Fixed-combination Gel of Clindamycin phosphate (Clindamycin 1%) and Tretinoin (0.025%) applied topically once-daily Duration of treatment: 12 weeks

DISPENSED: Rx

INITIAL SUBMISSION DATES:

Received by CDER: 16 October 2009
 Received by DAIOP: 15 January 2010
 Received by Reviewer: 15 January 2010
 Review Completed: 10 May 2010

RELATED DOCUMENTS: NDA 50-803 SN000

REMARKS:

VELTIN GEL is the subject of a 505(b)(2) New Drug Application of the Food, Drug and Cosmetic Act in accordance with Title 21 of the Code of

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Federal Regulations, §314.50. The Division of Dermatologic and Dental Drug Products requests a review of the proposed Clinical Microbiology subsection of the Clinical Pharmacology section of the proposed package insert. No Microbiology data were submitted with this application since the Applicant chooses not to pursue an antibacterial claim for this product. Microbiological studies were not performed by the Applicant for clindamycin phosphate and tretinoin as a fixed-combination product.

CONCLUSION AND RECOMMENDATION:

The Applicant does not seek antibacterial claims for VELTIN GEL. In this submission the Applicant provides no clinical microbiology data from clinical trials conducted with their product. This Reviewer recommends **APPROVAL** of this application.

While clindamycin is not the preferred treatment option for *S. aureus* infections, clindamycin is approved for the treatment of uncomplicated skin and skin structure infections (uSSSI) as well as community acquired pneumonia (CAP) caused by *S. aureus*. The development of resistance to clindamycin from the use of this antibiotic to treat acne may have serious consequences for patients who may require subsequent treatment of pharyngitis particularly for those patients that rely on the use of macrolide therapy due to penicillin allergy, community acquired pneumonia due to *Streptococcus pneumoniae* and hospital-associated pneumonia due to *S. aureus*. In addition, because clindamycin is used for the treatment of abscesses due to anaerobes the use of clindamycin to treat acnes is best avoided due to the potential development of clindamycin resistance in anaerobes.

However, while clindamycin is not the preferred treatment option for *S. aureus* infections, clindamycin is approved for the treatment of uncomplicated skin and skin structure infections (uSSSI) as well as community acquired pneumonia (CAP) caused by *S. aureus*. Consequently, 12 weeks of treatment for severe inflammatory acne is of concern, as this drug may not be useful to these patients should they develop uSSSI or CAP later. Clindamycin resistance has also been seen in

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macrolide-resistant *Streptococcus pyogenes*, an organism responsible for pharyngitis and cellulitis (uSSSI).

There is concern that the development of resistance to clindamycin from the use of this antibiotic to treat acne may have serious consequences for patients who may require subsequent treatment of pharyngitis due to *Streptococcus pyogenes* particularly for those patients that rely on the use of macrolide therapy due to penicillin allergy, community acquired pneumonia due to *Streptococcus pneumoniae* and *S. aureus* as well as hospital-associated pneumonia due to *S. aureus*. In addition, because clindamycin is used for the treatment of abscesses due to anaerobes the use of clindamycin to treat acnes is best avoided due to the potential development of clindamycin resistance in these organisms.

Due to the potential for the development of clindamycin resistance, this Reviewer recommends the following statement be included in the WARNINGS and PRECAUTIONS section of the package insert:

WARNINGS and PRECAUTIONS

The use of clindamycin to treat acnes may result in the development of clindamycin resistance in a variety of bacteria. One form of resistance seen in *Staphylococcus aureus*, and *Streptococcus pyogenes* is inducible clindamycin resistance. The presence of inducible resistance will result in these bacteria becoming resistant to clindamycin during treatment. Inducible-clindamycin resistance requires a special laboratory test to detect. To avoid treatment failure the presence of inducible clindamycin resistance in *S. aureus* and *S. pyogenes* should be determined prior to treating infections caused by these bacteria with clindamycin (See Pharmacology 12.4).

APPLICANT'S PROPOSED MICROBIOLOGY SECTION OF THE PACKAGE INSERT

(b) (4)



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(b) (4)

**AGENCY VERSION OF THE MICROBIOLOGY SUBSECTION OF
THE PACKAGE INSERT**

12.4 Microbiology

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

*Inducible Clindamycin Resistance (see **Warnings and Precautions**)*

The treatment of acnes with antimicrobials is associated with the development of antimicrobial resistance in *P. acnes* and other patient associated bacteria (e.g. *Staphylococcus aureus*, *Streptococcus pyogenes*). Inducible clindamycin resistance has been observed in *Staphylococcus aureus* and *Streptococcus pyogenes*. The presence of the clindamycin may result in these bacteria developing inducible resistance to clindamycin. This resistance is not detected by routine susceptibility testing. Its detection requires a special laboratory test¹. Therefore consultation with the microbiology laboratory is recommended prior to using clindamycin to treat *S. aureus* or *S. pyogenes* infections in any patient population including acne patients using clindamycin to determine if inducible clindamycin resistance is present. The clinical significance of this inducible resistance in acnes patients is not known.

WARNINGS and PRECAUTIONS

The use of clindamycin to treat acnes may result in the development of clindamycin resistance in a variety of bacteria. One form of resistance seen in *Staphylococcus aureus*, and *Streptococcus pyogenes* is inducible clindamycin resistance. The presence of inducible resistance will result in these bacteria becoming resistant to clindamycin during treatment. Inducible-clindamycin resistance requires a special laboratory test to detect. To avoid treatment failure the presence of inducible clindamycin resistance in *S. aureus* and *S. pyogenes* should be determined prior to treating infections caused by these bacteria with clindamycin (See Pharmacology 12.4).

REFERENCE

CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 20th Informational Supplement. CLSI document M100-S20. CLSI, Wayne, PA 19087, 2010.

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INTRODUCTION

Acne vulgaris is a skin disorder of the sebaceous follicles that commonly occurs in adolescence and in young adulthood. While the exact cause of acne vulgaris is not understood some factors that may contribute to the condition have been identified. Acne vulgaris lesions may occur because local metabolism of sex hormones stimulates an increase in the size of the sebaceous glands resulting in the production of excess sebum, the lipid rich secretion of the sebaceous gland. Sebum is believed to be a pivotal player in acne pathogenesis and provides a growth medium for *Propionibacterium acnes*.

The major factors contributing to the pathogenesis are hyperkeratinization, obstruction of sebaceous follicles resulting from abnormal keratinization of the infundibular epithelium, stimulation of sebaceous gland secretion by androgens, and microbial colonization of pilosebaceous units by the anaerobic bacterium *P. acnes*, which promotes perifollicular inflammation. The increased activity of sebaceous glands, elicited by androgen, causes proliferation of *P. acnes* in the pilosebaceous ducts. The organism possesses a ribosome-rich cytoplasm and a relatively thick cell wall and produces several biologically active mediators that may contribute to inflammation, for instance, by promoting leukocyte migration and follicular rupture. In inflamed lesions, neutrophils and macrophages infiltrate around hair follicles and sometimes phagocytosis *P. acnes*. The immunologic responses to *P. acnes* involve the humoral, cell-mediated, and complement pathways.

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The suppression of *P. acnes* is associated with clinical improvement although absolute numbers of *P. acnes* do not correlate with the severity of acne.

Topical clindamycin phosphate is prescribed for the treatment of mild to moderate acne vulgaris. Clindamycin phosphate is a lincosamide antibiotic with activity against a variety of Gram-positive bacteria as well as Gram-positive and Gram-negative anaerobes. Clindamycin binds to the 50S subunit of the bacterial ribosome and inhibits early stages of protein synthesis. It is primarily a bacteriostatic agent. Clindamycin phosphate is biologically inactive being hydrolyzed to the active form of free clindamycin. This hydrolyzation occurs following oral, parenteral and topical administration. The literature indicates that the MIC₉₀ range for clindamycin against *P. acnes* is in the range of ≤ 0.06 to 0.125 $\mu\text{g/mL}$. Studies of the use of clindamycin and erythromycin for the treatment of acne vulgaris have documented the development of resistance to both antimicrobials between 6 to 18 weeks. Resistance to clindamycin is associated with cross-resistance to erythromycin.

Tretinoin, also a component of this product, is a natural metabolite of vitamin A (retinol). Topical tretinoin was first used for the treatment of acne in 1969, and currently is used in a range of concentrations (0.01 to 0.1%) in the treatment of acne vulgaris, under the brand names of Retin A[®], Retin A[®] Micro, Avita[®] (gel or cream). The Applicant did not indicate in this submission whether tretinoin has any microbiological activity. A review of the literature did not find any evidence that tretinoin (all-trans-retinoic acid) has antibacterial activity.

The Applicant, Connetics Corp., submits this New Drug Application (NDA), for VELTIN Gel under section 505(b)(2) of the Food, Drug and Cosmetic Act in accordance with Title 21 of the Code of Federal Regulations, §314.50. No microbiology information has been submitted because the Applicant makes no antibacterial claims for their product.

PRECLINICAL EFFICACY

MECHANISM OF ACTION

Clindamycin phosphate is the water soluble ester of clindamycin and phosphoric acid. Until hydrolyzed to the active form clindamycin, clindamycin phosphate has little or no antibacterial activity. Hydrolysis occurs naturally upon absorption *in vivo*. Clindamycin acts as a broad-spectrum antibiotic by binding to the 50S subunits of susceptible bacteria and preventing the elongation of peptide chains by interfering with peptidyl transfer, hence, suppressing protein synthesis. Clindamycin phosphate is a bacteriostatic agent.

Tretinoin (all-trans-retinoic acid) is a natural oxidative metabolite of vitamin A (retinol). It is normally found at low concentrations (4-14 nmol/L) in the human circulation and

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bound to albumin. Tretinoin is a comedolytic agent and its effectiveness has been attributed to its ability to reduce follicular hyperkeratinization and inhibit inflammatory reactions. It has also been reported that tretinoin not only normalizes hyperkeratinization, but also promotes drainage of pre-existing comedones and inhibits the formation of new ones. Follicles become unplugged and the environment within the follicles becomes less favorable for the growth of *P. acnes* and the consequent production of proinflammatory mediators.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

According to the Applicant, the antimicrobial activity of VELTIN GEL was not tested because the nonclinical pharmacology of clindamycin is well characterized and the addition of tretinoin is not expected to interfere in the antibacterial effect of clindamycin. The Applicant did not include *in vitro* microbiological data regarding clindamycin phosphate and tretinoin gel as a fixed-combination product from clinical studies. In response to the previous Reviewer's request for information regarding the *in vitro* activity of clindamycin and tretinoin as a fixed-combination product against *P. acnes* from published literature, the Applicant responded that their literature search did not reveal any published studies investigating the *in vitro* activity of clindamycin and tretinoin as a fixed-combination product against *P. acnes*. The Applicant, however, provided sufficient information from the literature on the clinical use of clindamycin and tretinoin as a fixed-combination product for the treatment of acne. The Applicant also provided a published paper describing an *in vitro* study that involved tretinoin-clindamycin as a combined product. In this study, the authors reported that clindamycin does not interfere with tretinoin's anti-inflammatory activity and immuno-modulatory effects, nor the antibacterial activity of clindamycin against *P. acnes* is compromised.

Clindamycin phosphate was approved in the US as a topical treatment for acne vulgaris in 1987 as CLEOCIN ®T. Studies that demonstrated the effectiveness of clindamycin phosphate (1%) as treatment for mild to moderate acne vulgaris have been reported in the literature. Clindamycin has been shown to have *in vitro* activity against a variety of Gram-positive bacteria and strictly anaerobic Gram-positive and Gram-negative bacteria, including *P. acnes*. *P. acnes* is an anaerobic Gram-positive non-sporeforming bacillus that has been associated with acne vulgaris infections. Review of the literature shows *in vitro* susceptibility of *P. acnes* isolates to clindamycin; the MIC₉₀ value of 0.125 µg/mL for clindamycin against *P. acnes* has been reported. Studies reported in the literature have shown that the topical preparation of clindamycin phosphate in 1% concentration may inhibit growth of *P. acnes*.

ANTIMICROBIAL RESISTANCE

Macrolides, lincosamides and streptogramin (MLS) antibiotics are structurally unrelated; however, they are related microbiologically because of their similar mode of action. MLS antibiotics inhibit bacterial protein synthesis by binding to 23S rRNA, which is a part of

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the large ribosomal subunit. They have a spectrum of activity directed against Gram-positive cocci, Gram-negative cocci and intra-cellular bacteria such as chlamydiae and rickettsiae.

Resistance to MLS antibiotics occur either through target site modification, efflux of antibiotics, or drug modification. In target-site modification, methylation of the A2058 residue, located in the conserved domain V of 23s rRNA takes place, which leads to cross resistance and results in the formation of the phenotype of resistance pattern known as MLS_B. This phenotype is encoded by erythromycin ribosome methylases (*erm*) genes that have been reported from a wide variety of microorganisms.

Staphylococci

Clindamycin is used in the treatment of skin and soft-tissue infections, caused by the staphylococcal species. Good oral absorption makes this drug an important option in outpatient therapy or as a follow-up after intravenous therapy. Clindamycin is also used as an alternative for patients who are allergic to penicillin.

The expression of the MLS_B phenotype can be constitutive (MLS_B c) or inducible (MLS_B i). Inducible resistance is observed when the inactive mRNA produced by the production of methylases becomes active in the presence of an inducer, while active methylase mRNA is produced in strains where constitutive expression is seen. The strains carrying the inducible *erm* gene are resistant to the inducer and remain susceptible to non inducer macrolides and lincosamides. Low levels of erythromycin is an inducer of the MLS_B i phenotype, which forms the basis of the D-test, a double disk diffusion test in which the zone of inhibition around the clindamycin disk is blunted on the side facing the erythromycin disk (2).

Treatment of an infection using clindamycin or any non inducer macrolide, caused by a strain carrying inducible *erm* gene, can lead to clinical failure. Constitutive mutants can be selected *in vitro* in the presence of clindamycin or any other non inducer macrolide as they are widespread among methicillin-resistant strains.

Streptococcus pyogenes

Other than spontaneous mutation, resistance to macrolides in *S. pyogenes* can be the result of at least five different mechanisms. These mechanisms are methylation of 23S rRNA (mono- or bi-methylation of a single adenosine residue at position A-2058 or A-2059 residues), efflux, mutation, hydrolysis by esterases and inactivation by 2' OH-phosphorylase or 2'OH-glycoside transferase. A sixth possible mechanism is mutation in 23S rRNA or the L4 ribosomal protein.

The two primary mechanisms of macrolide resistance in *S. pyogenes* are efflux (encoded by *mefA*) and target modification due to ribosomal methylation (encoded by *ermB* or *ermA*). Isolates with *mefA* gene have a pattern of resistance known as the M phenotype;

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they are macrolide resistant but lincosamide and streptogramin susceptible. *S. pyogenes* isolates with the *ermB* gene are usually resistant to macrolides, lincosamides, and streptogramin B antibiotics, a resistance pattern known as constitutive MLS_B. Isolates with the *ermA* gene typically have an inducible MLS_B phenotype that requires exposure to a macrolide inducer before clindamycin resistance becomes evident. The *S. pyogenes* possessing this form of resistance can often be detected in the laboratory with the D test (3).

Propionibacterium acnes

In recent years, the development of resistance of *P. acnes* to topical antibiotics which may result in loss of efficacy has been emerging. In 1979, combined resistance to erythromycin and clindamycin in cutaneous *Propionibacterium* was first reported in the US in 20% of acne patients using topical formulation of either drug. In a study over a 10-year period, investigators reported that the proportion of patients carrying strains resistant to one or more commonly used anti-acne antibiotics showed a steady increase. Resistance to erythromycin was the most common and most erythromycin-resistant strains were cross-resistant to clindamycin.

A microbiological definition of clindamycin resistant *P. acnes* associated with acne vulgaris is difficult to establish. Some investigators have considered *P. acnes* with a clindamycin MIC of ≥ 8 $\mu\text{g/mL}$ to be clindamycin resistant. However, such an association is confounded by an inability to precisely determine antibiotic concentrations in normal or inflamed follicles. Clinical response to treatment with clindamycin is most often used as a marker for susceptibility or resistance of the *P. acnes* to clindamycin since routine culture of acne lesions to obtain *P. acnes* is not commonly done and thus there are no *P. acnes* isolates to test for their susceptibility to clindamycin or other antimicrobials. Treatment failure is often taken as an indication of the presence of clindamycin resistant *P. acnes* while treatment success is taken as an indication that resistance to clindamycin was not present or was present in only a small percentage of the total *P. acnes* population.

Numerous studies have shown that topical application of clindamycin or other antimicrobials to acne lesions generally results in an increase in the concentration of the antimicrobial over time that is necessary to inhibit growth of *P. acnes* or to kill it. This development of reduced susceptibility to clindamycin is not unique to drugs used to treat acnes but to antimicrobial use in general. The development of clindamycin resistance in other bacteria related to the presence of clindamycin resistance in *P. acnes* due to transfer of genetic transfer has not been shown to occur on the skin of individuals but is a possibility. Indeed a search of the literature did not find information to confirm that there has been resistance gene transfer between *P. acnes* and other facultative or anaerobic bacteria either *in vitro* or *in vivo*. Therefore it is postulated that if clindamycin resistance was to occur during the application of clindamycin to acne lesions the development of clindamycin resistant populations of bacteria would be as a result of selection of resistant

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bacteria from the overall clindamycin susceptible population of bacteria that are present, the development of resistance due primarily to exposure of the bacteria to subinhibitory concentrations of the clindamycin or both. Antimicrobial resistant populations of bacteria have been shown to occur in a variety of bacteria when they are exposed to subinhibitory concentrations of antimicrobials.

Reviewer's comments: Acne patients are a natural population in whom to study the long-term effects of antibiotic use (1). Tetracyclines and erythromycin are commonly used for the long-term treatment of acne vulgaris. Investigators have shown that *Propionibacterium acnes* and coagulase-negative staphylococci can quickly develop resistance to these antibiotics, resulting in therapeutic failure and the propagation of bacterial resistance on the skin and in the gastrointestinal flora.

In a study conducted on the effect of both oral and topical antibiotic treatment on patients with acne, Levy et al. examined the prevalence and resistance patterns of *Streptococcus pyogenes* and *Staphylococcus aureus* in the oropharynx of these individuals (1). Patients undergoing oral or topical antibiotic therapy in this study had more than a three fold increase in the prevalence *S. pyogenes* in their oropharynx compared with those not using any antibiotics. In addition, 85% of *S. pyogenes* cultures from those using antibiotics were resistant to at least one tetracycline antibiotic compared with 20% from those not using antibiotics. Of the patients undergoing oral or topical antibiotic therapy in this study, 22% had positive cultures of *S. aureus* in their oropharynx compared with 29% those not using any antibiotics. The investigators did not find any significant differences in *S. aureus* resistance patterns.

Note that those who were using only oral antibiotics as well as those using only topical antibiotics had similar increases in prevalence when compared with counterparts not using antibiotics. This indicates that *S. pyogenes* colonization of the oropharynx may be affected by multiple modes of antimicrobial administration. Just like oral antibiotics, topical antibiotics may preferentially eliminate particular bacteria thus causing shifts in the microbial flora that allow certain species, i.e. *S. pyogenes* to flourish when they might otherwise be restrained.

While clindamycin is not the preferred treatment option for *S. aureus* infections, clindamycin is approved for the treatment of uncomplicated skin and skin structure infections (uSSSI) as well as community acquired

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pneumonia (CAP) caused by *S. aureus*. The development of resistance to clindamycin from the use of this antibiotic to treat acne may have serious consequences for patients who may require subsequent treatment of pharyngitis particularly for those patients that rely on the use of macrolide therapy due to penicillin allergy, community acquired pneumonia due to *Streptococcus pneumoniae* and hospital-associated pneumonia due to *S. aureus*. In addition, because clindamycin is used for the treatment of abscesses due to anaerobes the use of clindamycin to treat acnes is best avoided due to the potential development of clindamycin resistance in anaerobes.

REFERENCES

1. Levy, RM, Huang EY, Roling D, Leyden JJ, Margolis DJ. 2003. Effect of Antibiotics on the Oropharyngeal Flora in Patients with Acne. *Arch Dermatol.* 139:467-71.
2. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 20th Informational Supplement. CLSI document M100-S20. CLSI, Wayne, PA 19087, 2010.
3. Raney, PM, F Tenover, R Carey, et al. 2006. Investigation of inducible clindamycin and telithromycin resistance in isolates of β -hemolytic streptococci. *Diagn Microbiol Infect Dis* 55:213-218.

Peter Coderre, PhD
Microbiology Reviewer

For concurrence only:
FMarsik, Ph.D./TLMicro/HFD-
520
16 Jun 10 FIN FJM

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

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/s/

PETER E CODERRE
06/17/2010

FREDERIC J MARSIK
06/17/2010

NDA 50-803
Velac Gel
Connetics Corp
Clinical Microbiology Review

**DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS (HFD-520)
CLINICAL MICROBIOLOGY REVIEW CONSULTATION FOR HFD 540**

NDA 50-803

Date Completed: 31 January 2005

Date Company Submitted: 23 August 2004
Date Received: 31 August 2004
Date Assigned: 31 August 2004
Reviewer: Connie R. Mahon, MS

NAME AND ADDRESS OF APPLICANT:

Connetics Corp.
3290 West Bayshore Rd
Palo Alto, CA 94303

CONTACT PERSON:

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Vice-President, Regulatory Affairs
Connetics Corp.
Phone: 650-739-2930
Fax: 650-843-2802

DRUG PRODUCT NAME:

Proprietary Name: VELAC® GEL
Compendial Name: Clindamycin Phosphate, USP
Empirical formula: $C_{18}H_{34}ClN_2O_8PS$
Molecular wt: 504.97

Compendial Name: Tretinoin, USP
Empirical formula: $C_{20}H_{28}O_2$
Molecular wt: 300.44

PROPOSED INDICATION: Topical application for the treatment of acne vulgaris.

**PROPOSED DOSAGE FORM, DOSAGE, STRENGTH, ROUTE OF
ADMINISTRATION, AND DURATION OF TREATMENT**

Proposed dosage form: Fixed-combination Gel of Clindamycin phosphate and tretinoin
Strength and dosage: Clindamycin Phosphate (Clindamycin 1%) and Tretinoin (0.025%)
applied topically once-daily
Duration of treatment: 12 weeks

Dispensed: Prescription

RELATED DOCUMENTS REVIEWED: IND 65,369 S/N 0030

TYPE OF SUBMISSION: Microbiology Review Consultation for HFD 540

PURPOSE OF SUBMISSION: The Applicant, Connetics Corp, submits an original NDA for for VELAC ®Gel, a fixed-combination prescription drug product. The product consists of clindamycin phosphate (clindamycin 1%) and tretinoin (0.025%) formulated in a gel for once-daily topical treatment of acne vulgaris.

The Applicant files the NDA under section 505(b)(2) and refers to published literature on certain nonclinical studies, including fertility and peri-/post-natal development although there is currently no approved product that is a combination of clindamycin phosphate and tretinoin that may serve as a reference listed drug.

The Division of Dermatologic and Dental Drug Products has requested a review and assessment of the proposed Clinical Microbiology subsection of the Clinical Pharmacology section of the proposed draft label (package insert). There are no Microbiology data submitted with this application. Microbiological studies were not performed by the Applicant for clindamycin phosphate and tretinoin as a fixed-combination product.

SUMMARY AND RECOMMENDATION

Propionibacterium acnes is a strict anaerobic gram-positive bacillus that has been associated with acne vulgaris. Studies reported in the literature have found that combined therapy with topical tretinoin and topical clindamycin is effective in acne therapy. Review of the literature also shows *in vitro* susceptibility of *P acnes* to clindamycin; an MIC₉₀ of 0.125 µg/mL for clindamycin against *P. acnes* has been reported. The results of the clinical studies performed by the Applicant, VLC C 304 and VLC C 305, show that Velac Gel, a fixed-combination product of clindamycin (1%) and tretinoin (1%), met the primary and secondary efficacy evaluation criteria. Microbiology studies were not performed during the clinical studies.

From a microbiology perspective the product is approvable with the following changes to the “Indication” and “Microbiology” sections of the package insert (See Agency’s proposed “INDICATION” and “MICROBIOLOGY” sections of package insert below).

APPLICANT’S PROPOSED MICROBIOLOGY SECTION OF THE PACKAGE INSERT

(b) (4)

AGENCY'S PROPOSED CHANGE TO THE "MICROBIOLOGY" SECTION OF THE PACKAGE INSERT

MICROBIOLOGY SECTION

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

The clindamycin component has been shown to have in vitro activity against *Propionibacterium acnes*, an organism which has been associated with *acne vulgaris*; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product.

Drug resistance

There are reports of an increase of P. acnes resistance to clindamycin in the treatment of acne. In patients with P. acnes resistance to clindamycin, the clindamycin component may provide no additional benefit beyond tretinoin alone."

INTRODUCTION

Velac Gel is a fixed-combination prescription drug product that consists of clindamycin phosphate (1% clindamycin) and tretinoin (0.025%) formulated in a gel for once-daily topical treatment of acne vulgaris. Clindamycin phosphate was first approved in the US for topical treatment of acne vulgaris in 1987 under the trademark of CLEOCIN®. Tretinoin has also been widely available in marketed products for topical application for over 30 years to treat a variety of dermatoses, including acne, photo aging, keloids, pigmentation disorders, and pre-neoplastic and neoplastic lesions.

According to the Applicant, Velac Gel was first developed and registered with the health authority in France by Yamanouchi Europe, B.V. Velac Gel was approved for marketing in France; however, Velac Gel was not distributed for business reasons. In 2002, Connetics, the Applicant of this NDA, purchased the exclusive rights to North America for this product with the intention of completing the necessary product evaluations required for marketing in the United States.

Acne vulgaris

Acne vulgaris is an inflammatory skin disorder characterized by the presence of eruptions, predominantly in the face, upper back and chest, made up of comedones, cysts, papules, and

pustules on an inflammatory base. The condition occurs usually during puberty and adolescence because of androgenic stimulation of sebum secretion, plugging of follicles by keratinization associated with *Propionibacterium acnes* proliferation.¹

The role of *P. acnes* in acne vulgaris, has been reported in the literature.² *P. acnes* is a strict anaerobic gram-positive non-spore-forming bacillus and a member of the normal skin flora. Proliferation of *P. acnes* is considered to be critical for the development of inflammatory lesions. The blocked follicles become an ideal anaerobic culture environment which contains nutrients including lipid substrates. *P. acnes* metabolizes sebaceous triglycerides, consumes the glycerol fraction, and discards free fatty acids. As a consequence, this organism is able to produce neutrophil chemical attractants, activate complement, and in general, stimulate inflammatory response. Although the suppression of *P. acnes* has been associated with clinical improvement, the absolute numbers have not been correlated with the severity of the disease.^{3,4}

Treatments for acne vulgaris

Historically, anti-acne agents have included topical or systemic antibiotics or application of retinoids. Topical antibiotics have been helpful for inflammatory acne and have been used for treatment of acne vulgaris. These agents include erythromycin, clindamycin, sodium sulfacetamide and salicylic acid. Benzoyl peroxide is a topical anti-bactericidal that reduces the population of *P. acnes* in the sebaceous follicles by generating reactive oxygen. Other topical antibiotics reduce the population and demonstrate anti-inflammatory properties by suppressing chemotaxis and decreasing the percentage of pro-inflammatory free fatty acids in surface lipids.⁵

Erythromycin and clindamycin topical agents have been used in combination with benzoyl peroxide or tretinoin. Tretinoin, as a comedolytic agent, acts by normalizing follicular keratinization, promoting drainage of pre-existing comedones while inhibiting the formation of new ones. Published studies have reported the efficacy of topical tretinoin when used in combination with either topical benzoyl peroxide, topical (e.g. clindamycin) or oral antibiotics (e.g. tetracycline). One added benefit of such combinations apparently is the obvious decrease of irritation from tretinoin when a topical antimicrobial agent is added.^{6,7,8}

IN VITRO INFORMATION

Clindamycin

Antimicrobial Spectrum of Activity

Clindamycin phosphate was approved in the US as a topical treatment for acne vulgaris in 1987 as CLEOCIN ®T. Studies that demonstrated the effectiveness of clindamycin phosphate (1%) as treatment for mild to moderate acne vulgaris have been reported in the literature^{9,10} Clindamycin

phosphate is a bacteriostatic agent that has been shown to have activity against a variety of gram-positive bacteria and strictly anaerobic gram-positive and gram-negative bacteria, including *P. acnes*. *P. acnes* is an anaerobic gram-positive non-sporeforming bacillus that has been associated with acne vulgaris infections. Review of the literature shows in vitro susceptibility of *P. acnes* isolates to clindamycin; an MIC₉₀ of 0.125 µg/mL for clindamycin against *P. acnes* has been reported.¹¹ Studies reported in the literature have shown that the topical preparation of clindamycin phosphate in 1% concentration may inhibit growth of *P. acnes*.¹⁰

Mechanism of action

Clindamycin phosphate is the water soluble ester of clindamycin and phosphoric acid. Until hydrolyzed to the active form clindamycin, clindamycin phosphate has little or no antibacterial activity. Hydrolysis occurs naturally upon absorption in vivo. Clindamycin acts as a broad-spectrum antibiotic by binding to the 50S subunits of susceptible bacteria and preventing the elongation of peptide chains by interfering with peptidyl transfer, hence, suppressing protein synthesis.¹²

In Section 2.6.2.2.2 in this submission, the Applicant provides the literature summary describing the *in vitro* spectrum of antimicrobial activity of clindamycin and the anti-comedolytic activity of tretinoin. The Applicant has provided sufficient information from the literature on the mechanism of action and *in vitro* antimicrobial properties of clindamycin.

Tretinoin

Section 2.4.2.2 provides the literature summary of the pharmacologic properties of tretinoin. Tretinoin (all-trans-retinoic acid) is a natural oxidative metabolite of vitamin A (retinol). It is normally found at low concentrations (4-14nmol/L) in the human circulation and bound to albumin. Tretinoin is a comedolytic agent and its effectiveness has been attributed to its ability to reduce follicular hyperkeratinization and inhibit inflammatory reactions. It has also been reported that tretinoin not only normalizes hyperkeratinization, but also promotes drainage of pre-existing comedones and inhibits the formation of new ones. Follicles become unplugged and the environment within the follicles becomes less favorable for the growth of *P. acnes* and the consequent production of proinflammatory mediators.⁶

According to the Applicant, the antimicrobial activity of Velac Gel was not tested because the nonclinical pharmacology of clindamycin is well characterized and that the addition of tretinoin is not expected to interfere in the antibacterial effect of clindamycin. The Applicant did not include *in vitro* microbiological data regarding clindamycin phosphate and tretinoin gel as a fixed-combination product from clinical studies. In response to the Reviewer's request for information regarding the *in vitro* activity of clindamycin and tretinoin as a fixed-combination product against *P. acnes* from published literature, the Applicant responded that their literature search did not reveal any published studies investigating the *in vitro* activity of clindamycin and tretinoin as a

fixed- combination product against *P. acnes*. The Applicant, however, provided sufficient information from the literature on the clinical use of clindamycin and tretinoin as a fixed combination product for the treatment of acne. The Applicant also provided a published paper describing an *in vitro* study that involved tretinoin-clindamycin as a combined product. In this study, the authors reported that clindamycin does not interfere with tretinoin's anti-inflammatory activity and immuno-modulatory effects, nor the antibacterial activity of clindamycin against *P. acnes* is compromised.¹³

Antimicrobial resistance

In recent years, the development of resistance of *P acnes* to topical antibiotics which may result in loss of efficacy has been emerging. In 1979, combined resistance to erythromycin and clindamycin in cutaneous propionibacteria was first reported in the US in 20% of acne patients using topical formulation of either drug.¹ In a study over a 10-year period, investigators reported that the proportion of patients carrying strains resistant to one or more commonly used anti-acne antibiotics showed a steady increase. Resistance to erythromycin was the most common and most erythromycin-resistant strains were cross-resistant to clindamycin.^{14,15}

IN VIVO INFORMATION

SYNOPSIS AND REPORTS OF CONTROLLED CLINICAL STUDIES

(Section 2.7.3)

The Applicant reports two controlled Phase 3 clinical studies, VLC C 304 and VLC.C 305, to evaluate the safety and efficacy of Velac Gel as compared to Clindamycin Gel, Tretinoin Gel, and Vehicle Gel in male and female subjects with acne vulgaris.

For both studies, the Investigator's Static Global Assessment (ISGA), and Subject's Global Assessment (SGA) as standards measure, are used. The definitions of ISGA and SGA scoring scale for both studies are shown on Tables 1 and 2, respectively.

Table 1 Investigator's Static Global Assessment (Section 2.7.3.1 page 5)

Score*	Definition
Grade 0	Normal, clear skin with no evidence of acne vulgaris

Grade 1	Skin almost clear: rare non-inflammatory lesions present, with rare non-inflamed papules (papules most be resolving and may be hyper-pigmented, though not pink) requiring no further treatment in the investigator's opinion
Grade 2	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulo-cystic lesions)
Grade 3	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules and there may or may not be 1 small nodulo-cystic lesion
Grade 4	Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulo-cystic lesions
Grade 5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulo-cystic lesions

*The ISGA is an overall assessment of subject's facial acne vulgaris

The scores are dichotomized in the data analysis into "success" –defined as a score of 0-1 and "failure" scores of 2-5. Subject's Global Assessment score definition is shown on Table 2.

Table 2 Subject's Global Assessment (Section 2.7.3.1 page 6)

Score	Definition
Grade 0	My face is basically free of acne, with only an occasional blackhead and/or whitehead
Grade 1	My face has several blackheads and/or whiteheads and small pimples, but there are no tender deep-seated bumps or cysts
Grade 2	My face has several blackheads and/or whiteheads and small pimples, but may have one tender deep-seated bumps or cysts
Grade 3	My face has many blackheads and/or whiteheads many medium-to large-seized pimples, and perhaps a few deep-seated bumps or cysts
Grade 4	My face has many blackheads and/or whiteheads , and several to many medium-to large-seized pimples, and deep-seated bumps or cysts dominate

Synopsis for Study No. VLC C.304 (2.7.3.2.1 page 11)

This study is a Phase III, multi-center, randomized, double-blind, active-and vehicle-controlled

study of the safety and efficacy of VELAC® GEL (clindamycin phosphate (clindamycin 1%) and tretinoin (0.025%) for the treatment of acne vulgaris. The objectives of the study were to 1) demonstrate the superiority of Velac Gel vs. Clindamycin Gel and Tretinoin Gel on 2 of 3 lesion counts (total, inflammatory, and non-inflammatory), 2) demonstrate overall greater improvement or superiority in the ISGA for Velac Gel vs. Clindamycin Gel and Tretinoin Gel 3) demonstrate the superiority in the ISGA for Velac Gel vs. Vehicle Gel on 2 of 3 lesion counts (total, inflammatory, and non-inflammatory) and the ISGA, and 4) evaluate the safety of Velac Gel in subjects ages 12 years old or older with acne vulgaris.

Study period: 16 December 1002- 20 January 2004

Number of subjects enrolled: 1083

Gender: 481 males, 602 females

Age: 12 – or older

Ethnicity: 674 Caucasians, 234 Black, 114 Hispanic, and 61 Other

Duration of treatment: 12 weeks

Criteria for Evaluation

Primary endpoints were the percent reduction in lesion counts (total, inflammatory, non-inflammatory) from baseline to week 12 (end of treatment) and the proportion of subjects who had an investigator's "Static Global Assessment" score of 0 or 1 at week 12. The secondary endpoints were the absolute reduction in lesion counts (total, inflammatory, and non-inflammatory) from baseline to week 12; and the change in the subject's "Global Assessment" from baseline to week 12; the proportion of subjects with a Subject's Global assessment score of 0 or 1 at week 12 and the time to a 50% reduction in total lesion counts.

Primary Efficacy Results (Section 2.7.3.2.1. pages 12-20)

In the clinical study, VLC C 304, to demonstrate efficacy, the following endpoints are assessed: 1) the per cent reduction in lesion counts (total, inflammatory, and non-inflammatory) from Baseline to Week 12 (end of treatment) and 2) the proportion of subjects who had an ISGA score of 0 or 1 at Week 12. (0 is clear and 1 is almost clear).

Table 3 shows the results of the per cent reduction in lesion counts and the p-values for the comparisons between Velac Gel and Clindamycin Gel, Tretinoin Gel, and Vehicle Gel. Mean per cent reduction in lesion counts comparing Velac Gel and Clindamycin Gel with regards to the total lesions and non-inflammatory lesions show statistically significant difference (p value=<0.0001). The Applicant reports that the mean percent reduction in inflammatory lesion counts for Velac Gel is greater than Clindamycin Gel, however, the statistical significance (p=0.0503) is borderline. For all lesion count categories (total, non-inflammatory and inflammatory), the mean per cent reduction in lesions counts between Velac Gel and Vehicle Gel are statistically significant (p=<0.0001). Similarly, the mean per cent reductions in all three lesion counts when Velac Gel is

compared with Tretinoin Gel show statistical significance.

Table 3 Per Cent Reduction in Lesion Counts from Baseline to Week 12 (Study VLC C 304)
 Section 2.7.3.2.1. page13

	Velac Gel	Clindamycin Gel	Tretinoin Gel	Vehicle Gel
Number of Subjects	309	311	310	153
Total Lesions				
% reduction (std)	46.2(35.3)	33.8(33.2)	35.6(30.8)	20.0(38.7)
p-value ^a		<0.0001	<0.0001	<0.0001
		<0.0001	<0.0001	<0.0001
Inflammatory Lesions				
% reduction (std)	52.3(36.2)	46.4(38.7)	39.3(37.4)	27.2(44.6)
p-value		0.0503	<0.0001	<0.0001
		0.0529	<0.0001	<0.0001
Non-inflammatory Lesions				
% reduction (std)	41.5(43.5)	25.0(41.3)	32.9(36.0)	14.3(49.3)
p-value		<0.0001	0.00065	<0.0001
		<0.0001	0.0002	<0.0001

^a p-values are derived from a parametric ANOVA model (top value) and a rank-transformed model (bottom value) ($\alpha=0.04806$) with terms for treatment and center and compare Velac Gel against Clindamycin Gel, Tretinoin Gel, and Vehicle gel, respectively.

Efficacy is also assessed using the ISGA at Baseline and at Weeks 2,4,8, and 12 (end of treatment). Treatment success is defined as an ISGA score of 0 or 1 at Week 12. The pair-wise comparisons of treatment groups, Velac Gel and Clindamycin Gel, Tretinoin Gel, and Vehicle Gel show statistical significance for all comparisons. The number of subjects in the ITT population and the proportion (%) of subjects with success at Week 12 is shown on Table 4.

Table 4 Subjects with Success at Week 12 using ISGA (Study VLC C 304)

Section 2.7.3.2.1. page 15

	Velac Gel	Clindamycin Gel	Tretinoin gel	Vehicle Gel
Number of Subjects	309	311	310	153
Success (SGA of 0 or 1)	107(35%)	66(21%)	60(19%)	19(12%)
p-value ^a		0.0002	<0.0001	<0.0001

^a p-values are derived from Cochran-Mantel-Haenszel test ($\alpha=0.05$) stratified by center and compare Velac Gel against Clindamycin Gel, Tretinoin Gel, and Vehicle gel, respectively

Reviewer's Comments:

These results show that the difference in mean per cent reduction in total lesions and non-inflammatory lesions shown by Velac Gel is statistically significant when compared with those by Clindamycin Gel, Tretinoin Gel and Vehicle Gel. However, Velac Gel has a similar effect as Clindamycin Gel on inflammatory lesions. The results of this clinical study indicate that Velac Gel has met the primary endpoints set forth (% reduction in two out of three lesion counts).

The results of the ISGA study where the proportions of subjects within each treatment groups attained treatment success (ISGA 0 or 1) are compared suggest that Velac Gel has met the criteria set for this endpoint.

Secondary Efficacy Results

Section 2.7.3.2.2 pages 16-20

The secondary efficacy analyses considered three endpoints: 1) the absolute reduction in lesion counts (total, inflammatory, and non-inflammatory) from Baseline to Week 12 (EOT), 2) the proportion of subjects who had a Subjects Global Assessment (SGA) score of 0 or 1 at Week 12 (considered success) and 3) the time to a 50% reduction in total lesion counts.

Mean Absolute Reduction

The Applicant reports the mean absolute reduction in total lesion counts as 35.0, 23.7, 25.6, and 12.9 for Velac Gel, Clindamycin Gel, Tretinoin Gel and Vehicle Gel groups, respectively. For inflammatory lesion counts, mean absolute reductions were 13.1, 11.3, 9.5, and 6.8; and for non-inflammatory lesion counts, 21.9, 12.4, 16.1, and 6.1, in all respective treatment groups. The Applicant's parametric analyses of these results show that Velac Gel group is superior to both the Clindamycin Gel and Tretinoin Gel groups in the mean absolute reduction of total lesion counts ($p<0.0001$ and $p<0.0001$ respectively; inflammatory ($p=0.0210$ and $p<0.0001$, respectively); and non-inflammatory ($p<0.0001$ and $p=0.0021$, respectively).

Subject's Global Assessment

In the Subject's Global Assessment (SGA), the Applicant reports that the proportions of subjects who attained success for the SGA at Week 12 are 60% , 51%, 46% and 37% for Velac Gel, Clindamycin Gel, Tretinoin Gel, and Vehicle gel, respectively. The results show that the difference in success rate between subject groups is significant when Velac Gel is compared to Clindamycin Gel, Tretinoin Gel, (p=0.0338 and p=0.0007, respectively) and Vehicle Gel (p<0.0001).

Subjects with a 50% reduction in Total Lesion Counts Over time

The proportion of subjects with a 50% reduction in total lesion counts is reported by the Applicant as consistently higher at each study visit in the Velac Group compared to Clindamycin Gel, Tretinoin Gel, and Vehicle Gel groups. In this assessment study, results show that at Week 12 (end of treatment), 59%, 43%, 45%, and 31% of the subjects showed 50% reduction in total lesion counts in the Velac Gel, Clindamycin Gel, Tretinoin Gel, and Vehicle Gel groups, respectively. The Applicant also reports that the proportion of subjects with a 50% reduction in total lesion counts is consistently higher at each visit in the Velac gel group compared to Clindamycin Gel, Tretinoin Gel, and Vehicle Gel. For all comparisons, the time to 50% reduction in total lesion counts for Velac Gel versus Clindamycin Gel, Tretinoin Gel, and Vehicle Gel is statistically significant (p<0.0001 , p=0.0004, and p<0.0001, respectively).

Conclusion

These results indicate that Velac Gel has met the secondary efficacy endpoints set forth.

Synopsis for Study No. VLC C.305 (Section 2.7.3.2.2 pages 20-30)

This study is a Phase III, multi-center, randomized, double-blind, active-and vehicle-controlled study of the safety and efficacy of VELAC® GEL (clindamycin phosphate (clindamycin 1%) and tretinoin (0.025%) for the treatment of acne vulgaris. The objectives of the study were to 1) demonstrate the superiority of Velac Gel vs. Clindamycin Gel and Tretinoin Gel on 2 of 3 lesion counts (total, inflammatory, and non-inflammatory), 2) demonstrate overall greater improvement or superiority in the ISGA for Velac Gel vs. Clindamycin Gel and Tretinoin Gel 3) demonstrate the superiority in the ISGA for Velac Gel vs. Vehicle Gel on 2 of 3 lesion counts (total, inflammatory, and non-inflammatory) and the ISGA, and 4) evaluate the safety of Velac Gel in subjects ages 12 years old or older with acne vulgaris.

Study period: 16 December 1002- 21 January 2004

Number of subjects enrolled: 1136

Gender: 542 males, 594 females

Age: 12 – or older

Ethnicity: 768 Caucasians, 203 Black, 104 Hispanic, and 61 Other

Duration of treatment: 12 weeks

Criteria for Evaluation

Primary endpoints were the percent reduction in lesion counts (total, inflammatory, non-inflammatory) from baseline to week 12 (end of treatment) and the proportion of subjects who had an investigator’s “Static Global Assessment” score of 0 or 1 at week 12. The secondary endpoints were the absolute reduction in lesion counts (total, inflammatory, and non-inflammatory) from baseline to week 12; and the change in the subject’s “Global Assessment” from baseline to week 12; the proportion of subjects with a Subject’s Global assessment score of 0 or 1 at week 12 and the time to a 50% reduction in total lesion counts.

Primary Efficacy Results (Section 2.7.3.2.2.1 pages 22-30)

In the clinical study, VLC C 305, to demonstrate efficacy, the following endpoints are assessed: 1) the per cent reduction in lesion counts (total, inflammatory, and non-inflammatory) from Baseline to Week 12 (end of treatment), and 2) the proportion of subjects who had an ISGA score of 0 or 1 at Week 12. (0 is clear and 1 is almost clear).

Table 5 shows the results of the per cent reduction in lesion counts and the p-values for the comparisons between Velac Gel and Clindamycin Gel, Tretinoin Gel, and Vehicle Gel. Mean per cent reduction in lesion counts comparing Velac Gel and Clindamycin Gel with regards to the total lesions, inflammatory lesion and non-inflammatory lesions show statistically significant difference (p value= <0.0001 (p=0.0303). For all lesion count categories (total, non-inflammatory and inflammatory), the difference in mean per cent reduction in lesions counts between Velac Gel and Vehicle Gel are statistically significant (p=<0.0001). Similarly, the mean per cent reductions in all three lesion counts when Velac Gel is compared with Tretinoin Gel show statistical significance.

Table 5 Per Cent Reduction in Lesion Counts from Baseline to Week 12 (Study VLC C 305)
(Section 2.7.3.2.2.1 page 23)

	Velac Gel	Clindamycin Gel	Tretinoin Gel	Vehicle Gel
Number of Subjects	325	324	325	162

Total Lesions				
% reduction (std)	51.1(28.4)	42.5(31.7)	44.9(31.0)	26.2(38.5)
p-value ^a		0.0001	0.0034	<0.0001
		0.0002	0.0029	<0.0001
Inflammatory Lesions				
% reduction (std)	54.5(36.5)	48.6(37.2)	47.2(33.9)	33.3(46.9)
p-value		0.0306	0.0041	<0.0001
		0.0209	0.0003	<0.0001
Non-inflammatory Lesions				
% reduction (std)	48.8(31.3)	37.8(39.7)	42.7(37.1)	22.5(45.3)
p-value		<0.0001	0.0121	<0.0001
		<0.0001	0.0271	<0.0001

^a p-values are derived from a parametric ANOVA model (top value) and a rank-transformed model (bottom value) ($\alpha=0.04806$) with terms for treatment and center and compare Velac Gel against Clindamycin Gel, Tretinoin Gel, and Vehicle gel, respectively.

Efficacy is also assessed using the ISGA at Baseline and at Weeks 2,4,8, and 12 (end of treatment). Treatment success is defined as an ISGA score of 0 or 1 at Week 12. The pair-wise comparisons of treatment groups, Velac Gel and Clindamycin Gel, Tretinoin Gel, and Vehicle Gel show statistical significance for all comparisons. The number of subjects in the ITT population and the proportion (%) of subjects with success at Week 12 is shown on Table 6.

Table 6 Subjects with Success at Week 12 using ISGA (Study VLC C 305) (Section 2.7.3.2.2.1 page 25)

	Velac Gel	Clindamycin Gel	Tretinoin gel	Vehicle Gel
Number of Subjects	325	324	325	162
Success (SGA of 0 or 1)	128(39%)	105(32%)	100(31%)	24(15%)
p-value ^a		0.0441	0.0108	<0.0001

^a p-values are derived from Cochran-Mantel-Haenszel test ($\alpha=0.05$) stratified by center and compare Velac Gel against

Clindamycin Gel, Tretinoin Gel, and Vehicle gel, respectively

Reviewer's Comments:

These results show that a significant difference in mean per cent reductions in total lesions, inflammatory lesions, and non-inflammatory lesions in Velac Gel when compared with Clindamycin Gel, Tretinoin Gel, and Vehicle Gel. The results of this clinical study suggest that Velac Gel has met the primary endpoints set forth.

The results of the ISGA study where the proportions of subjects within each treatment groups attained treatment success (ISGA 0 or 1) are compared suggest that Velac Gel has met the criteria set for this endpoint.

Secondary Efficacy Results

Section 2.7.3.2.2.2 (pages 26-30)

The secondary efficacy analyses considered three endpoints: 1) the absolute reduction in lesion counts (total, inflammatory, and non-inflammatory) from Baseline to Week 12 (EOT), 2) the proportion of subjects who had a Subjects Global Assessment (SGA) score of 0 or 1 at Week 12 (considered success) and 3) the time to a 50% reduction in total lesion counts.

Mean Absolute Reduction

The Applicant reports the mean absolute reduction in total lesion counts as 41.5, 32.6, 35.5, and 19.6, for Velac Gel, Clindamycin Gel, Tretinoin Gel and Vehicle Gel groups, respectively. For inflammatory lesion counts, mean absolute reductions were 14.7, 12.9, 12.5, and 8.6; for non-inflammatory lesion counts, 21.9, 12.4, 16.1, and 6.1, in all respective treatment groups. The Applicant's parametric analyses of these results show that Velac Gel group is superior to both the Clindamycin Gel and Tretinoin Gel groups in the mean absolute reduction of total lesion counts ($p < 0.0001$ and $p = 0.0048$ respectively; inflammatory ($p = 0.0235$ and $p = 0.0032$, respectively); and non-inflammatory ($p < 0.0001$ and $p = 0.0309$, respectively).

Subject's Global Assessment

In the Subject's Global Assessment (SGA), the Applicant reports that the proportions of subjects who attained success for the SGA at Week 12 are 63%, 55%, 56% and 44% for Velac Gel, Clindamycin Gel, Tretinoin Gel, and Vehicle gel, respectively. The results show that the difference in success rate between subject groups is significant when Velac Gel is compared to Clindamycin Gel, Tretinoin Gel, ($p = 0.0188$ and $p = 0.0478$, respectively) and Vehicle Gel ($p < 0.0001$).

Subjects with a 50% reduction in Total Lesion Counts Over time

The proportion of subjects with a 50% reduction in total lesion counts is reported by the Applicant as consistently higher at each study visit in the Velac Group compared to Clindamycin Gel, Tretinoin Gel, and Vehicle Gel groups. In this assessment study, results show that at Week 12 (end of treatment), 59%, 43%, 45%, and 31% of the subjects showed 50% reduction in total

lesion counts in the Velac Gel, Clindamycin Gel, Tretinoin Gel, and Vehicle Gel groups, respectively. The Applicant also reports that the proportion of subjects with a 50% reduction in total lesion counts is consistently higher at each visit in the Velac gel group compared to Clindamycin Gel, Tretinoin Gel, and Vehicle Gel. For the comparisons in the time to 50% reduction in total lesion counts for Velac Gel versus Clindamycin Gel, and Vehicle Gel ($p < 0.0045$ and $p < 0.0001$, respectively), the difference is statistically significant. However, the comparison between Velac Gel and Tretinoin shows a borderline statistical significance ($p = 0.0539$).

Reviewer's Comments:

The results from this study indicate that Velac Gel has met the secondary efficacy endpoints set forth.

OVERALL CONCLUSION

Propionibacterium acnes is a strictly anaerobic gram-positive bacillus that has been associated with acne vulgaris. Studies reported in the literature have found that combined therapy with topical tretinoin and topical clindamycin is effective in acne therapy. Review of the literature also shows *in vitro* susceptibility of *P. acnes* to clindamycin; an MIC₉₀ of 0.125 µg/mL for clindamycin against *P. acnes* has been reported. The results of the clinical studies performed by the Applicant, VLC C 304 and VLC C 305, show that Velac Gel, a fixed-combination product of clindamycin (1%) and tretinoin (1%), met the primary and secondary efficacy evaluation criteria. Microbiology studies were not performed during the clinical studies.

From a microbiology perspective the product is approvable with the following changes to the "Indication" and "Microbiology" sections of the package insert (See Agency's proposed "INDICATION" and "MICROBIOLOGY" sections of package insert below).

APPLICANT'S PROPOSED MICROBIOLOGY SECTION OF THE PACKAGE INSERT



AGENCY'S PROPOSED CHANGE TO THE "MICROBIOLOGY" SECTION OF THE PACKAGE INSERT

MICROBIOLOGY SECTION

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

The clindamycin component has been shown to have in vitro activity against *Propionibacterium acnes*, an organism *which has been associated with acne vulgaris*; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product.

Drug resistance

There are reports of an increase of P. acnes resistance to clindamycin in the treatment of acne. In patients with P. acnes resistance to clindamycin, the clindamycin component may provide no additional benefit beyond tretinoin alone.”

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¹⁵Ross, JI et al. Clinical resistance to erythromycin and clindamycin in cutaneous propionibacteria isolated from acne patients is associated with mutations in 23S rRNA. 1997. *Antimicro Agents and Chemo.* 41:1162-1165.

Connie R. Mahon, MS, CLS (NCA)
Microbiologist, HFD-520
31 January 2005

Fred Marsik, Ph.D.
Acting Microbiology Team Leader
HFD-520
Finalized 2/3/05

HFD-520/Dept/Dir/L. Gavrilovich

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/s/

Connie Mahon
5/9/05 01:35:07 PM
MICROBIOLOGIST

Frederic Marsik
5/9/05 01:38:56 PM
MICROBIOLOGIST

Lillian Gavrilovich
5/9/05 04:27:03 PM
MEDICAL OFFICER

45 DAY MEETING CHECKLIST

MICROBIOLOGY FILEABILITY

On initial overview of the NDA application:

- | | YES/NO |
|--|---------------|
| 1. Is the microbiologic section of the NDA organized in a manner to allow substantive review to begin? | N/A |
| 2. Is the microbiologic section of the NDA indexed and paginated in a manner to allow substantive review to begin? | N/A |
| 3. Is the microbiology section and other microbiologically pertinent sections of the NDA legible so that substantive review can begin? | N/A |

HAS THE APPLICANT SUBMITTED:

- | | |
|--|-----|
| 4. <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains and using necessary numbers of approved laboratories to meet current Divisional standards for approvability of the product based on the submitted draft labeling? | N/A |
| 5. any required animal model studies necessary for approvability of the product based on the submitted draft labeling? | N/A |
| 6. draft breakpoints and interpretive criteria in a manner consistent with contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin? | N/A |
| 7. all special studies/data requested by the Division during pre-submission discussions? | N/A |
| 8. draft labeling consistent with 201.56 and 201.57, current Divisional policy, and the design of the development package? | YES |

(b) (4)

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2 of 2

YES/NO

9. FROM A MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? **IF NO, GIVE REASONS BELOW.** YES

Comments:

There are no Microbiology data submitted in this NDA for review. Based on the information provided in the Pre-NDA briefing package for review consultation , from the Microbiology perspective, the Reviewer finds the Microbiology section in the proposed package insert adequate. However, the Reviewer has requested that the Sponsor provide information regarding the *in vitro* activity of clindamycin and tretinoin as a fixed-combination product against *P. acnes* from published literature.

Connie R. Mahon 10/13/2004

Reviewing Microbiology Officer

Fred Marsik Ph.D. 10/14/2004
Supervisory Microbiology Officer

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/s/

Connie Mahon
10/14/04 01:35:33 PM
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10/14/04 01:42:45 PM
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Lillian Gavrilovich
10/15/04 03:00:21 PM
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