CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-801

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-709**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**12/23/03**
PRODUCT:	**Clindamycin phosphate foam, 1%**
INTENDED CLINICAL POPULATION:	**Patients with acne vulgaris**
SPONSOR:	**Connetics Corporation**
DOCUMENTS REVIEWED:	**Vol. 1-3**
REVIEW DIVISION:	**Division of Dermatologic and Dental Drug Products (HFD-540)**
PHARM/TOX REVIEWER:	**Jill C. Merrill**
PHARM/TOX SUPERVISOR:	**Paul C. Brown**
DIVISION DIRECTOR:	**Jonathan Wilkin, M.D.**
PROJECT MANAGER:	**Melinda Harris**

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability - ——— for the treatment of acne vulgaris is approvable from a pharmacological/toxicological perspective

B. Recommendation for nonclinical studies – No additional nonclinical studies are recommended for ——— at this time.

C. Recommendations on labeling –Sponsor proposed labeling is acceptable from a pharmacological/toxicological perspective.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings – Repeat dose toxicity studies following topical application of clindamycin phosphate have been conducted in various species. Dermal effects were minimal, but some species may develop diarrhea and this has been associated with mortality. See section C.

B. Pharmacologic activity – Clindamycin phosphate is a lincosamide antibiotic

C. Nonclinical safety issues relevant to clinical use - The most pronounced toxicity associated with clindamycin has been pseudomembranous colitis. This is believed to be caused by the overgrowth of a toxin producing *Clostridium difficile*. However, because systemic exposure following topical application of clindamycin is low, it is not anticipated that subjects receiving treatment with clindamycin phosphate will be affected. A warning about this adverse effect is included in the labels of currently approved formulations of clindamycin and will be included in the ——— label.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-709
Review number: 1
Sequence number/date/type of submission: 000/12-22-03/original NDA submission
005/05-05-04/ labeling amendment
006/08-06-04/labeling amendment
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: Connetics Corporation, Palo Alto, CA 94303
Manufacturer for drug substance: ⊏ ⊐

Reviewer name: Jill C. Merrill
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: 9/02/04

Drug:

Trade name: ———

Generic name: clindamycin phosphate

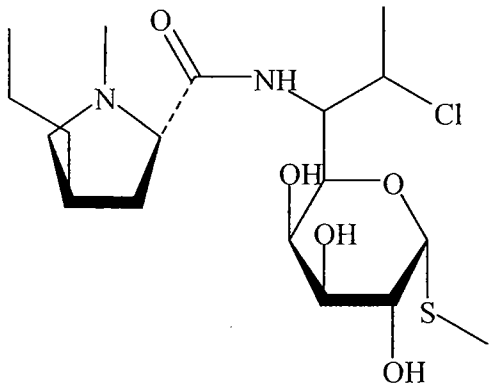
Chemical name: Methyl-7-chloro-6,7,8-trideoxy-6-(1-methyl-4-*trans*-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate)

(2S-*trans*)-Methyl-7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)-carbonyl]amino]-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate)

CAS registry number: 24729-96-2

Molecular formula/molecular weight: $C_{18}H_{34}ClN_2O_8PS$, MW= 504.97

Structure:



Relevant INDs/NDAs/DMFs:
IND 64,577 (Clindamycin phosphate)
IND 56,487 (Clindagel)
NDA 50-782 (Clindagel)
DMF —— (Clindamycin phosphate)

Drug class: lincosamide antibiotic

Intended clinical population: patients with acne vulgaris

Clinical formulation: foam containing sufficient clindamycin phosphate to provide 1% clindamycin

Ingredient	Amount w/w %
Clindamycin phosphate, USP	
Cetyl alcohol, NF	
Dehydrated alcohol, USP	
Polysorbate 60, NF	
Potassium hydroxide, NF	
Propylene glycol, USP	
Purified water, USP	
Stearyl alcohol, NF	

Route of administration: topical to the skin

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-709 are owned by Connetics Corporation or are data for which Connetics Corporation has obtained a written right of reference. Any information or data necessary for approval of NDA 21-709 that Connetics Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Connetics Corporation does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-709.

Introduction and drug history: The sponsor has submitted this NDA under section 505(b)2 of the FD&C Act and is referring to the approved NDA for Clindagel® (clindamycin phosphate gel) Topical Gel, 1% as evidence of safety for this drug (NDA 50-782). The sponsor has conducted a 12-week phase 3 clinical study of the safety and efficacy of clindamycin phosphate foam (1%) versus Clindagel® for the treatment of Acne Vulgaris. The study demonstrated the non-inferiority of clindamycin phosphate foam versus Clindagel® and the superiority of clindamycin phosphate foam versus vehicle foam based on lesion counts and an Investigator's Static Global Assessment. At the pre-NDA meeting (11-19-03) the sponsor indicated that the nonclinical data to support product approval would be based on publications and the FDA's findings of safety as established by the clinical bridge. They also indicated that in the NDA submission they would be including tabulated summaries for the toxicology studies, but the pharmacology and pharmacokinetics studies would be covered by a written summary. The agency responded that this would be acceptable, provided an adequate clinical bridge was established to Clindagel®.

Studies reviewed within this submission:

none

Studies not reviewed within this submission: N/A

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Clindamycin phosphate is the water-soluble ester of clindamycin and phosphoric acid. It has little or no antibacterial effect *in vitro*, but it is rapidly hydrolyzed both *in vitro* and *in vivo*, to the active compound, clindamycin base. Clindamycin binds to the 50S subunit of bacterial ribosomes and thereby interferes with bacterial protein synthesis. Clindamycin is primarily bacteriostatic. Clindamycin is active against aerobic gram positive cocci and most anaerobic gram negative organisms. Its activity against the anaerobe *Propionibacterium acnes* may account for its effectiveness in the treatment of acne vulgaris.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Clindamycin binds to the 50S subunit of bacterial ribosomes and thereby interferes with bacterial protein synthesis.

Drug activity related to proposed indication: The efficacy of clindamycin in the treatment of acne lies in its ability to inhibit the growth of *P. acnes*. Overgrowth of *P. acnes* and the ensuing host inflammatory response are believed to be important in the pathogenesis of acne. Blocking protein synthesis has been reported to directly decrease the production of pro-inflammatory mediators, including lipase, hemolysin, glycocalyx matrix, Shiga-like toxin, and streptolysin S by susceptible bacteria.

2.6.2.3 Secondary pharmacodynamics

The ability of clindamycin to interfere with bacterial protein synthesis may have downstream effects other than inhibition of bacterial growth. Clindamycin's protein inhibitory activity blocks the production of lipases and inflammatory mediators by bacteria. It has been demonstrated that subinhibitory concentrations of clindamycin, as well as other antibiotics, can block the production of lipases by *P. acnes*. Other studies have demonstrated that subinhibitory concentrations of clindamycin can inhibit the production of hemolysin in *Esherichia coli*, the synthesis of the glycocalyx matrix in *Staphylococci,* Shiga-like toxin release by *E. coli* and streptolysin S production by bacteria. Clindamycin's protein inhibitory activity may also alter the bacterial surface in a manner that makes them be recognized differently by host defenses. For example, subinhibitory concentrations of clindamycin have been reported to alter bacteria, making them more susceptible to killing by polymorphonuclear neutrophils. In summary, clindamycin's ability to inhibit bacterial protein synthesis leads to inhibition of inflammatory mediator production, thus potentially contributing to an ameliorating effect on the inflammatory component of acne.

2.6.2.4 Safety pharmacology

A transient neuromuscular blockade is a recognized side effect of clinical use of antibiotics, including clindamycin. Extensive analysis of the blockade has led to the conclusion that clindamycin exerts its main effect post-synaptically at the neuromuscular junction, with a minor component of the inhibition also occurring pre-synaptically. The basis for these effects has been determined to be the lipophilic nature of the structure of

clindamycin, which allows the molecule to compete with calcium for entry into nerve terminals, resulting in interference with nerve transmission. The effect of clindamycin on neuromuscular transmission has potential relevance to gastrointestinal smooth muscle function and the development of enterocolitis. However, because systemic exposure following topical application of clindamycin is low, it is not anticipated that subjects receiving treatment with clindamycin phosphate will be affected.

2.6.2.5 Pharmacodynamic drug interactions

No studies to address pharmacodynamic drug interactions were included in this submission.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

This section is not applicable.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Studies in rats and dogs show that clindamycin is readily absorbed from the gastrointestinal tract and is excreted in the urine and feces. In rats, the products excreted in the urine were 53% unchanged clindamycin, 31% clindamycin sulfoxide and 15% N-demethyl clindamycin. In dogs, the products excreted in the urine were 36% unchanged clindamycin, 28% clindamycin sulfoxide, 28% clindamycin glucuronide and 9% N-demethyl clindamycin. Topical application in the rat and pig show that clindamycin can be retained in the skin and is released into the blood for several days after drug application.

Absorption of clindamycin from topical formulations has been measured in humans and ranges from undetectable up to approximately 7.5% of the applied clindamycin. In humans approximately 10% of clindamycin administered is excreted unchanged in the urine. Clindamycin is metabolized in humans to N-demethyl clindamycin and clindamycin sulfoxide, which are excreted in the urine and bile.

2.6.4.2 Methods of Analysis

This section is not applicable.

2.6.4.3 Absorption

In nonclinical studies, topical application of clindamycin phosphate and clindamycin HCl has resulted in minimal drug absorption, compared to absorption following oral, *i.v., i.m., i.p.*, and *s.c.* administration. Gray *et al.* investigated the percutaneous absorption of clindamycin HCl in mini-pigs (*Int. J. Dermatol.* (1983) 22: 314-317). Half of the pigs were white, the remainder black. A 3% aqueous formulation, containing 5% (w/v) propylene glycol and 70% (v/v) isopropyl alcohol, was applied twice daily for 21 days

for a total of 43 treatments. The daily dose ranged from 7.33-10.26 mg/kg. Skin samples were taken at 4 h and at 5 days post-dose. Higher concentrations of antibiotic bioactivity (µg/g) were detected in sections containing epidermis than in those containing both epidermis and dermis at both 4 h and 5 days. In addition, black skinned pigs retained higher levels of antibiotic in the skin at 5 days. Very low bioactivity (0.13-0.63 µg/mL) was found in urine samples up to 97 h post-treatment. No evidence of dermal irritation was observed by visual inspection or microscopically.

2.6.4.4 Distribution

Distribution studies following dermal application of clindamycin have not been performed. A distribution profile similar to that observed following systemic dosing is expected following topical application, although at much lower levels. In a 21-day dermal irritation study in Sprague Dawley rats using 3% clindamycin phosphate applied to the intact or abraded skin three times daily for a total of 65 doses bioactivity at termination was present in all tissues and body fluids tested (*Int. J. Dermatol.* (1983) 22: 314-317). By 5 days following the last dose, residual bioactivity remained only in treated skin, urine, and long bones. The tissue distribution of clindamycin was studied in cats after multiple oral doses (*J. Vet. Pharmacol. Ther.* (1990) 13:270-277). Eighteen cats were randomly allocated into two blocks with three treatment groups and dosed orally with clindamycin aqueous solution for 10 days at a dosage rate of 5.5 mg/kg twice daily (Group 1), 11 mg/kg twice daily (Group 2), and 22 mg/kg once daily (Group 3). Approximately 2 h after the last dose, all cats were euthanized, and blood and tissues were taken for clindamycin analysis. Clindamycin was extracted from tissues using solid-phase extraction columns, followed by microbiological assay. All cats remained clinically healthy throughout the study. Serum concentrations of clindamycin at necropsy were 3.47± 1.35, 5.41± 1.47, and 6.47± 1.94 µg/mL in Groups 1, 2, and 3, respectively. Urine concentrations were 34.1± 22.7, 103.0± 45.3, and 116.0 ± 64.5 µg/mL, in the three groups, respectively. Bile concentrations were 15.0 µg/g (n=1) in Group 1, 93.5 and 109 µg/g (n=2) in Group 2, and 114 µg/g (n=1) in Group 3. Aside from urine and bile, the highest tissue to serum ratio was found in lung, followed by the spleen and liver. The tissue to serum ratio was > 1 in kidney, colon, jejunum, heart, and bone marrow, and < 1 in bone, CSF, brain, and skeletal tissue.

2.6.4.5 Metabolism

No studies on the metabolism of clindamycin have been conducted following topical dermal administration. Metabolic studies have been conducted following oral, *i.v.*, and *i.m.* administration of clindamycin phosphate or clindamycin hydrochloride. If systemic exposure does occur following topical administration of Clindamycin phosphate foam, the metabolic pathway would be expected to be similar to that observed following systemic dosing, but at much lower levels. The metabolism of clindamycin was studied in 12 female Sprague Dawley rats administered 100 mg/kg clindamycin HCl orally every day for 1 month (*J. Pharm. Sci.* (1973) 62:1265-1269). Tritium-labeled drug (6 µCi) was given on the first and last days. Urine specimens were collected once a day using metabolism cages. Thin layer chromatography, silica gel, chromatography, mass

spectrometry, and analysis of radioactivity of urine extracts demonstrated that 53.36% of the radioactivity in rat urine was unchanged free clindamycin, 31% was clindamycin sulphoxide, and 15.1% was N-demethylclindamycin. Analysis of radioactivity in pooled urine collected on the first and last days of chronic administration showed no differences, indicating that chronic administration of clindamycin did not modify metabolism of the drug. In another experiment, clindamycin metabolism was studied in three male beagle dogs following single daily oral doses of 500 mg clindamycin HCl in capsules for 7 days (*J. Pharm. Sci.* (1973) 62:1657-1662). Urine samples were collected once a day using metabolism cages. Urine samples containing radioactive clindamycin and metabolites from a previous experiment were added to the pooled urine to monitor separation of metabolites by thin layer chromatography. An average of 35.69% of the total radioactivity excreted in urine was unchanged drug. The remaining consisted of 27.57% clindamycin sulphoxide, 27.58% clindamycin glucuronide, and 9.16% N-demethylclindamycin.

2.6.4.6 Excretion

Excretion studies following topical dermal application of clindamycin have not been conducted, but patterns of excretion are expected to be similar to those found following systemic dosing. The absorption and excretion of clindamycin was studied in female Sprague Dawley rats following oral and *i.p.* administration of radiolabeled clindamycin HCl (*J. Pharm Sci.* (1973) 62:1265-1269). Tritium-clindamycin HCl at a dose of 1.54 mg and 18.7 mg of carrier drug were administered in a volume of 1.5 mL via stomach tube, to three rats, and 1.85 mg of tritium-labeled drug and 28.40 mg of cold drug was injected *i.p.* in 0.5 mL. Urine and feces samples were collected for 14 days. One third of the total radioactivity was excreted in the urine and two-thirds in the feces, independent of the route of administration. Following oral administration, 27.04% of the radioactivity was excreted in the urine, and 68.47% in the feces. Following *i.p.* injection, 27.73% of the total radioactivity was excreted through the kidney and 67.76% in the feces. Eighty-six percent of the radioactivity in the urine was excreted in the first 48 h following both routes of administration. Ninety percent of the fecal radioactivity was recovered only after 120 h, indicating a slower rate of excretion.

2.6.4.7 Pharmacokinetic drug interactions

No studies to address pharmacokinetic drug interactions were included in this submission.

2.6.4.8 Other Pharmacokinetic Studies

One *in vitro* study was conducted by Connetics to examine the percutaneous absorption and skin distribution profiles of clindamycin when applied as clindamycin phosphate foam to support the formulation selection. Two commercially available clindamycin products, a gel formulation (Clindagel 1%) and a solution (Cleocin T 1% Solution), were used as comparators in this study. Human skin was obtained from cosmetic surgery procedures, dermatomed to 0.25 mm thickness, and mounted in specially designed diffusion cells. Clindamycin, in one of the three formulations, was applied to the skin

and the dermal receptor solution was collected every 4 h for 24 h. The amount of clindamycin in the receptor fluid after 24 h was greatest from the solution (0.39% ± 0.04%), followed by the foam (0.16% ± 0.02%), and lastly from the gel (0.05% ± 0.04%). The amount of clindamycin in the epidermis was found to be similar for all three formulations (5.35-5.78%). In the dermis the amount of clindamycin was similar for the foam and solution (3.08% and 3.33%, respectively), while a greater amount of clindamycin was present from the gel formulation (5.45%).

2.6.4.9 Discussion and Conclusions

The bioavailability and potency of topical preparations are influenced by both the active ingredient and the components of the formulation. Percutaneous absorption of topical formulations of clindamycin has been shown to be either extremely limited or below the limit of detection by standard analytical methods. In a recently completed clinical study (CLN.C.001) systemic absorption of clindamycin from the foam formulation (clindamycin phosphate foam) was lower than from the comparator drug, Clindagel. While limited, absorbed clindamycin would be expected to be cleared mainly by the liver. It is not anticipated that clindamycin phosphate foam would lead to significantly different, or new, ADME characteristics.

2.6.4.10 Tables and figures to include comparative TK summary

This section is not applicable.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

This section is not applicable.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

The most pronounced toxicity associated with clindamycin has been pseudomembranous colitis. This is believed to be caused by the overgrowth of a toxin producing *Clostridium difficile* (*Gastroenterology* (1978) 75:778-782; *N Engl J Med* (1978) 298:531-534). Absorption of clindamycin phosphate from topical application may be sufficient to cause colitis. While the rat and dog do not demonstrate this toxicity, it has been observed in hamsters, rabbits and humans. In the hamster, all animals given 40, 10 or 1 mg/kg topically for 2 weeks died from colitis. Four of seven animals given 0.1 mg/kg also died (*Arch Dermatol* (1979) 115:580-581). A warning about this adverse effect is included in the labels of currently approved formulations of clindamycin.

Long term studies in rats and dogs have been conducted with clindamycin hydrochloride and clindamycin palmitate hydrochloride (*Arch Dermatol* (1979) 115:580-581; *Toxicol Appl Pharmacol* (1972) 21:516-531). The maximum tolerated dose of clindamycin hydrochloride in a one year rat study was between 300 and 600 mg/kg. No specific morphologic alteration attributed to treatment with clindamycin hydrochloride was identified. Clindamycin palmitate hydrochloride doses of 100, 300 and 600 mg/kg were well tolerated by rats in a six month study.

Acute dermal toxicology:

The single dose toxicity of topically applied clindamycin phosphate has been assessed in two rabbit studies, which were performed in support of the topical lotion (Cleocin T Topical Lotion, 1%, NDA 50-600, 1985) and topical gel (Cleocin T Gel, 1%, NDA 50-615) formulations of clindamycin phosphate. In a study in 5 male and 5 female rabbits, clindamycin phosphate lotion at a dose of 2 g/kg was applied topically to the abraded skin on the back, under occlusion, for 24 h. No compound-related dermal irritation or signs of systemic toxicity were reported at the end of the 14-day study period. No gross lesions were observed at necropsy. In another study in rabbits (5/sex), the toxicity of clindamycin phosphate gel was evaluated following a single topical dose of 2 g/kg to abraded skin on the backs. Application sites were occluded for 24 h, and then scored for irritation, and the animals were observed for clinical signs of toxicity. No mortality or compound-related clinical signs were recorded. Slight to moderate erythema was noted along the abraded marks. At necropsy, no lesions were noted upon gross examination.

Repeat dose topical toxicology:

A 21 day dermal irritation study in Sprague Dawley rats was performed using 3% clindamycin phosphate, which was applied to the intact or abraded skin three times daily (*Int J Dermatol* (1983) 22:314-317). At termination, antibiotic activity was present in all tissues and body fluids tested. By 5 days following the last dose, residual antibiotic activity remained in treated skin, urine, and long bones. No irritation by gross or histological examination was observed at the dermal test site. The skin of rats subjected to abrasion prior to treatment healed normally during the treatment period. Hematology and organ weights were normal.

A 21 day dermal irritation study was conducted in pigs using clindamycin HCl, at 3% in a vehicle containing 5% propylene glycol, 70% isopropyl alcohol, and water (*Int J Dermatol* (1983) 22:314-317). Treatment was applied twice daily to the clipped back skin of three white Yorkshire pigs and three black Hampshire pigs. Skin from black pigs retained more antibiotic activity at 5 days. There was no evidence of dermal irritation. No mortality was reported.

It is well known that oral administration of clindamycin can induce diarrhea and occasionally enterocolitis in humans. Although rare, topical clindamycin use has been associated with these symptoms (*Cutis* (1983) 32: 415, 9, 24, 28). The gastrointestinal side effects are believed to occur as a result of clindamycin-induced suppression of

indigenous bacterial flora of the gut, allowing overgrowth of pathogenic anaerobes, such as Clostridia (*Probl. Vet. Med.* (1990) 2:330-347). Absorption of clindamycin phosphate from topical application may be sufficient to cause colitis. While the rat and dog do not demonstrate this toxicity, it has been observed in hamsters, rabbits, and humans. In the hamster, all animals given 40, 10, or 1 mg/kg topically for 2 weeks died from colitis. Four of seven animals given 0.1 mg/kg also died (*Arch. Dermatol.* (1979) 115:580-581). These side effects subside following discontinuation of clindamycin administration and treatment with antibiotics, such as vancomycin.

In conclusion, the ability of clindamycin to suppress the growth of indigenous flora of the gut and to interfere with intestinal motility may contribute to the colonization of the gut by toxigenic bacteria, including *C. difficile.* Production of toxins by *C. difficile* leads to the development of enterocolitis. Discontinuation of clindamycin administration and therapy with other antibiotics known to inhibit *C. difficile* growth, such as vancomycin (*Rev. Infect. Dis.* (1984) 6 suppl 1:S208-213) or tetracycline (*Arch. Dermatol.* (1979) 115:580-581), are effective means to treat clindamycin-induced enterocolitis. Labeling for clindamycin phosphate foam will include warnings regarding discontinuation of treatment in the event that diarrhea or other gastrointestinal symptoms occur.

Genetic toxicology:

The sponsor has not conducted any studies on the genetic toxicology of clindamycin phosphate. However, the label of the listed drug contains the following information:

Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Carcinogenicity:

Dermal carcinogenicity:
The sponsor has not conducted any studies on the dermal carcinogenic potential of clindamycin phosphate. However, the label of the listed drug contains the following information:

The carcinogenicity of a 1% clindamycin phosphate gel similar to Tradename was evaluated by daily application to mice for two years. The daily doses used in this study were approximately 3 and 15 times higher than the human dose of clindamycin phosphate from 5 milliliters of Tradename, assuming complete absorption and based on body surface area comparison. No significant increase in tumors was noted in the treated animals.

Photocarcinogenicity:
The sponsor has not conducted any studies on the photocarcinogenic potential of clindamycin phosphate. However, the label of the listed drug contains the following information:

A 1% clindamycin phosphate gel similar to Tradename caused a statistically significant shortening of the median time to tumor onset in a study in hairless mice in which tumors were induced by exposure to simulated sunlight.

Reproductive toxicology:

The sponsor has not conducted any studies on the reproductive toxicology of clindamycin phosphate. However, the label of the listed drug contains the following information:

Reproduction studies in rats using oral doses of clindamycin hydrochloride and clindamycin palmitate hydrochloride have revealed no evidence of impaired fertility.

Pregnancy: Teratogenic effects - Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin phosphate, clindamycin hydrochloride and clindamycin palmitate hydrochloride. These studies revealed no evidence of fetal harm. The highest dose used in the rat and mouse teratogenicity studies was equivalent to a clindamycin phosphate dose of 432 mg/kg. For a rat, this dose is 84 fold higher, and for a mouse 42 fold higher, than the anticipated human dose of clindamycin phosphate from Tradename based on a mg/m^2 comparison. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Special toxicology:

Three animal studies were performed by the sponsor with the clindamycin phosphate foam vehicle, but containing betamethasone valerate, 0.12%, to support the NDA for Luxiq (NDA 20- 934). The three studies were an acute dermal irritation study in rabbits, a skin sensitization study in guinea pigs and an acute eye irritation study in rabbits. Dr. Syed Alam reviewed these studies in IND 52,124/000. The betamethasone foam was not a skin irritant in the rabbit or a sensitizer in the guinea pig. The foam was a moderate eye irritant in the rabbit.

2.6.6.2 Single-dose toxicity

No new single-dose toxicity studies were submitted with this NDA submission.

2.6.6.3 Repeat-dose toxicity

No new repeat-dose toxicity studies were submitted with this NDA submission.

2.6.6.4 Genetic toxicology

No new genetic toxicology studies were submitted with this NDA submission.

2.6.6.5 Carcinogenicity

No new carcinogenicity studies were submitted with this NDA submission.

2.6.6.6 Reproductive and developmental toxicology

No new reproductive and developmental toxicology studies were submitted with this NDA submission.

2.6.7 TOXICOLOGY TABULATED SUMMARY – N/A

REFERENCES

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Gray JE, Weaver RN, Bollert JA *et al.* The oral toxicity of clindamycin in laboratory animals. *Toxicol Appl Pharmacol* 1972; **21**:516-531.

Sun FF. Metabolism of clindamycin II: Urinary excretion products of Clindamycin in rat and dog. *J Pharm Sci* 1973; **62**:1657-1162.

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OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

There does not appear to be any reason to expect the foam formulation of clindamycin phosphate to have greater toxicity than other previously approved topical formulations of clindamycin phosphate. All of the ingredients in the foam formulation have been used by the topical route before at the same or greater concentrations in approved products. Based on the nonclinical data available for clindamycin phosphate, NDA 21-709 is approvable from a pharmacology/toxicology.

Unresolved toxicology issues (if any):

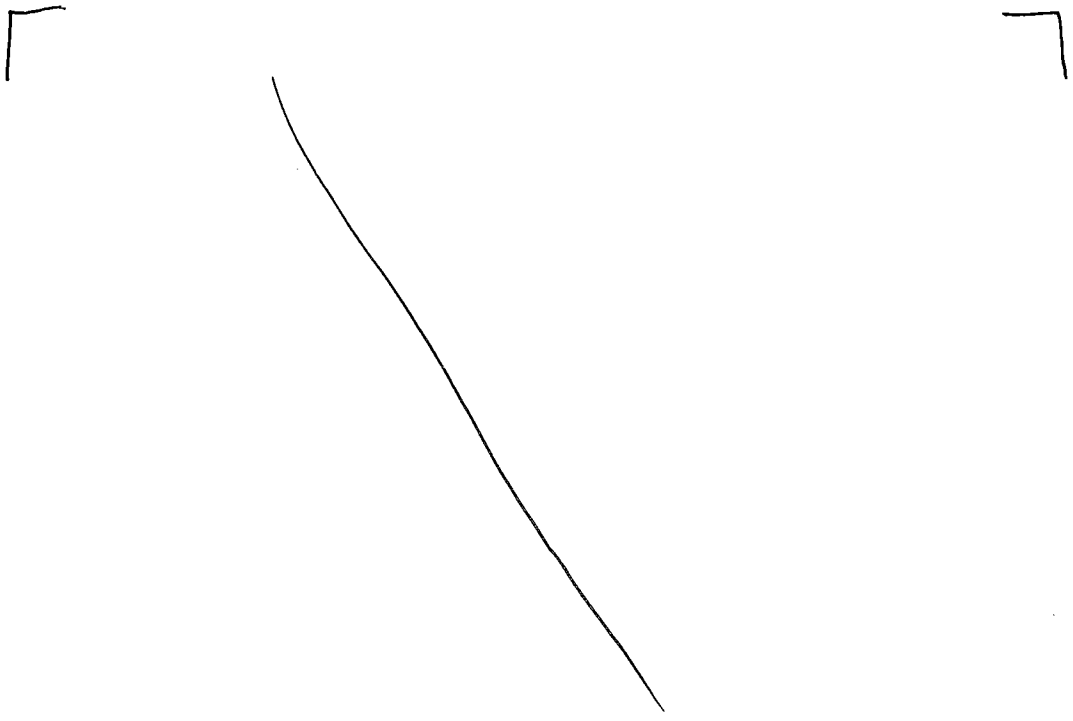
There are no unresolved toxicology issues for NDA 21-709, at this time.

Recommendations:

The sponsor proposed labeling matches the approved labeling for the listed drug. It is recommended that the sponsor proposed labeling be incorporated into the ——— label.

Sponsor proposed labeling:

Carcinogenesis, Mutagenesis, Impairment of Fertility



Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

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Jill Merrill
9/2/04 07:51:34 AM
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Paul Brown
9/2/04 10:25:55 AM
PHARMACOLOGIST

Division of Dermatologic and Dental Drug Products (HFD-540)
Pharmacology/Toxicology Checklist for NDA Filing Meeting

Date:	2-27-04
Reviewer:	Jill Merrill
NDA Number:	21-709
Drug Name:	Clindamycin phosphate foam, 1%
CAS Number:	24729-96-2
Drug Type:	3S
Drug Class:	Antibiotic
Indication:	Acne vulgaris
Route of Administration:	Topical
Date CDER Received:	12-29-03
User Fee Date:	10-29-04
Date of Draft Review:	8-1-04
Sponsor:	Connetics Corporation, Palo Alto, CA 94303

Fileability:
On initial overview of the NDA application:

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner to allow a substantive review to be completed? YES

The paper copy (Modules 1, 2, and 4) is acceptable. However, the electronic copy is not a stand alone document. It provides links to the cited references, but does not include the summary information and as such is incomplete.

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review? YES

The pharmacology/toxicology section of the paper copy is navigable. However, the electronic document is incomplete and lacks bookmarks which makes it difficult to process and navigate through the different sections.

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed? YES

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? N/A

This NDA for clindamycin phosphate foam is being submitted under Section 505(b)(2) of the Food, Drug and Cosmetic Act as a change in dosage form of the listed drug clindamycin phosphate gel. As

such, the sponsor plans to rely on the Agency's previous finding of safety and effectiveness for the listed drug and no new nonclinical data was either requested or submitted.

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? N/A

See response to question #4.

(6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57? YES

(7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? N/A

See response to question #4.

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route? N/A

See response to question #4.

(9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? N/A

See response to question #4.

(10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics? N/A

(11) Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? N/A

See response to question #4.

(12)	From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.	YES
(13)	If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify:	NO
(14)	Issues that should not be conveyed to the Sponsor:	N/A

_____
Pharmacology Reviewer

_____
Pharmacology Supervisor

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

/s/

Jill Merrill
3/1/04 01:48:52 PM
PHARMACOLOGIST

Paul Brown
3/1/04 02:03:15 PM
PHARMACOLOGIST