NDA 50-782

Target Research Associates
Attention: Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs
554 Central Avenue
New Providence, NJ 07974

Dear Dr. McCormack:

Please refer to your new drug application (NDA) dated January 27, 2000, received January 27, 2000, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tradename (clindamycin phosphate) Topical Gel, 1%.

We acknowledge receipt of your submissions dated February 28 and 29 (2), March 24, April 26 and 28 (2), May 16 and 25, July 17, 20 and 31, August 16 and 21, September 6, 14 and 18, October 9 and 31, and November 8, 15, 17, 20, 21 (2), and 22, 2000.

This new drug application provides for the use of Tradename (clindamycin phosphate) Topical Gel, 1%, for once a day treatment of acne vulgaris.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

According to "Guidance for Industry, Changes to an Approved NDA or ANDA," dated November 1999, you will need to submit a labeling supplement for alternative options for tradename. The reporting category for a tradename qualifies as a major change requiring a prior approval supplement per 21CFR 314.70(b)(3).

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 50-782." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have requested a waiver for pediatric studies on neonates, infants and children, because acne is not prevalent in the population from birth to 11 years, and clindamycin phosphate would not represent a substantive therapeutic benefit as an acne therapy for

that population. The Agency grants you a partial waiver for pediatric acne studies for the age group between birth and 11 years of age, under 21 CFR 314.55(c)(4).

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Indira Kumar, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

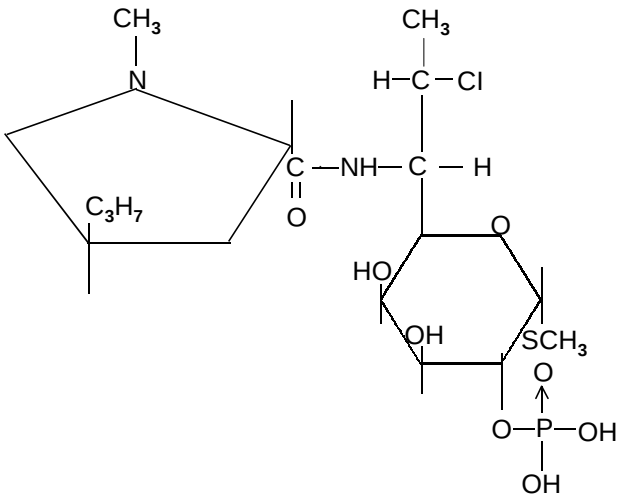
Enclosure

Tradename
(clindamycin phosphate gel) topical gel, 1%

For External Use

DESCRIPTION
Tradename (clindamycin phosphate gel) topical gel, 1%, a topical antibiotic, contains clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per gram in a gel vehicle consisting

of carbomer 941, methylparaben, polyethylene glycol 400, propylene glycol, sodium hydroxide, and purified water. Chemically, clindamycin phosphate is a water-soluble ester of the semi-synthetic antibiotic produced by a 7 (S)-chloro-substitution of the 7 (R)-hydroxyl group of the parent antibiotic, lincomycin, and has the structural formula represented below:



The chemical name for clindamycin phosphate is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate).

CLINICAL PHARMACOLOGY

Pharmacokinetics

In an open label, parallel group study of 24 patients with acne vulgaris, once-daily topical administration of approximately 3-12 grams/day of **Tradename** for five days resulted in peak plasma clindamycin concentrations that were less than 5.5 ng/ml.

Following multiple applications of **Tradename** less than 0.04 % of the total dose was excreted in the urine.

Microbiology

Although clindamycin phosphate is inactive in vitro, rapid in vitro hydrolysis converts this compound to clindamycin which has antibacterial activity. Clindamycin inhibits bacteria protein synthesis at the ribosomal level by binding to the 50S ribosomal subunit and affecting the process of peptide chain initiation. In vitro studies indicated that clindamycin inhibited all tested *Propionibacterium acnes* cultures at a minimum inhibitory concentration (MIC) of 0.4 μg/ml. Cross-resistance has been demonstrated between clindamycin and erythromycin.

CLINICAL STUDIES

In one 12-week, multicenter, randomized, evaluator-blind, vehicle-controlled, parallel comparison clinical trial in which patients used **Tradename** (clindamycin phosphate topical gel, 1%) once daily or the vehicle gel once daily, in the treatment of acne vulgaris of mild to moderate severity, **Tradename** applied once daily was more effective than the vehicle applied once daily. The mean percent reductions in lesion counts at the end of treatment in this study are shown in the following table:

Lesions	Tradename **QD** **N=162**	**Vehicle Gel QD N=82**
Inflammatory	51%	40% *
Noninflammatory	25%	12% *
Total	38%	27% *

*P< 0.05

There was a trend in the investigator's global assessment of the results which favored **Tradename** QD over the vehicle QD

In a contact sensitization study, four of the 200 subjects appeared to develop suggestive evidence of allergic contact sensitization to **Tradename**. There was no signal for contact sensitization in the clinical trials under normal use conditions.

INDICATIONS AND USAGE

Tradename is indicated for topical application in the treatment of acne vulgaris. In view of the potential for diarrhea, bloody diarrhea and pseudomembranous colitis, the physician should consider whether other agents are more appropriate. (See CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS.)

CONTRAINDICATIONS

Tradename is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

WARNINGS

Orally and parenterally administered clindamycin has been associated with severe colitis, which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should

be considered to establish a definitive diagnosis in cases of severe diarrhea. Antiperistaltic agents, such as opiates and diphenoxylate with atropine, may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parenteral therapy with clindamycin.

PRECAUTIONS
General
Tradename should be prescribed with caution in atopic individuals.

Drug Interactions
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility
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 a body surface area comparison. No significant increase in tumors was noted in the treated animals.

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.

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

Nursing Mothers
It is not known whether clindamycin is excreted in human milk following use of **Tradename**. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in children under the age of 12 have not been established.

Geriatric Use
The clinical study with **Tradename** did not include sufficient numbers of patients aged 65 and over to determine if they respond differently than younger patients.

ADVERSE REACTIONS
In the one well-controlled clinical study comparing **Tradename** and its vehicle, the incidence of skin and appendages adverse events occurring in ≥1% of the patients in either group is presented below:

	Number (%) of Patients	
Body System/Adverse Event	**Tradename QD (N=168)**	**Vehicle Gel QD (N=84)**
Skin and appendages disorders		
Dermatitis	0 (0.0)	1 (1.2)
Dermatitis contact	0 (0.0)	1 (1.2)
Dermatitis fungal	0 (0.0)	1 (1.2)
Folliculitis	0 (0.0)	1 (1.2)
Photosensitivity reaction	0 (0.0)	1 (1.2)
Pruritus	1 (0.6)	1 (1.2)
Rash erythematous	0 (0.0)	0 (0.0)
Skin dry	0 (0.0)	0 (0.0)
Peeling	1 (0.6)	0 (0.0)

Orally and parenterally administered clindamycin has been associated with severe colitis, which may end fatally.

Cases of diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of clindamycin and rarely with topical clindamycin (see WARNINGS). Abdominal pain and gastrointestinal disturbances, as well as gram-negative folliculitis, have also been reported in association with the use of topical formulations of clindamycin.

OVERDOSE
Topically applied **Tradename** may be absorbed in sufficient amounts to produce systemic effects (see WARNINGS).

DOSAGE AND ADMINISTRATION
Apply a thin film of **Tradename** once daily to the skin where acne lesions appear. Use enough to cover the entire affected area lightly.

Keep container tightly closed.

HOW SUPPLIED
Tradename containing clindamycin phosphate equivalent to 10 mg clindamycin per gram, is available in

the following sizes:
77 gram bottle - NDC xxxx-xxxx-xx
42 gram bottle - NDC xxxx-xxxx-xx
7.5 gram bottle - NDC xxxx-xxxx-xx (physician's sample, not for resale)
Store under controlled room temperature 20°C – 25°C (68°F to 77°F); excursions permitted between 15°C – 30°C (59°F to 86°F).
Do not store in direct sunlight.

CAUTION
Federal law prohibits dispensing without prescription.
Clindagel, LLC, Santa Rosa, CA, USA
Revised 11-22-00