CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-782

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Clindagel, LLC
4189 Chaparral Court
Santa Rosa, CA 95409

2. TELEPHONE NUMBER *(Include Area Code)*

(707) 483-7489

3. PRODUCT NAME Clindagel™ (Clindamycin phosphate gel) 1%

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

3885

6. LICENSE NUMBER / NDA NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Manager	January 6, 2000

FORM FDA 3397 (5/98)

WITHHOLD 2 PAGE (S)

(S)

Number of Pages Redacted 56

❖❖❖

Draft Labeling
(not releasable,

(S)

FOREIGN MARKETING HISTORY

Clindagel™ (clindamycin phosphate —— gel), 1% has not been marketed outside of the United States.

Commitment for the Submission of the Dermal Absorption Study Report

Clindagel LLC hereby commits that the final report for the study entitled "An Open-Label Randomized Study of the Comparative Absorption of Clindagel™ (QD) vs. Cleocin T (BID) in subjects with acne vulgaris (C-GEL-005) will be submitted to the Agency as a NDA amendment within three months of the initial NDA submission for Clindagel™. Clindagel LLC understands that failure to meet this commitment may affect the filing of the NDA for Clindagel™.

Gordon Dow, PharmD
Clindagel LLC

APPEARS THIS WAY
ON ORIGINAL

United States Patent Office 3,509,256 Patented Apr. 28, 1970

3,509,256

LINCOMYCIN-2-PHOSPHATE ANTIBIOTIC COMPOSITIONS AND PROCESS OF TREATMENT

Walter Morozowich and Donald J. Lusk, Kalamazoo, Mich., assignors to The Upjohn Company, Kalamazoo, Mich., a corporation of Delaware

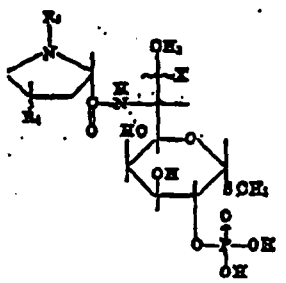
No Drawing. Continuation-in-part of application Ser. No. 602,116, Dec. 16, 1966. This application Jan. 8, 1969, Ser. No. 789,915

Int. Cl. A61k 27/00

U.S. Cl. 424—200 7 Claims

ABSTRACT OF THE DISCLOSURE

Compounds of the formula



wherein X is hydroxy, chlorine or bromine, R_1 is alkyl of C_{1-8}, cycloalkyl of C_{3-8}, or aralkyl of C_{7-12}, and R_2 is hydrogen, alkyl of C_{1-8}, cycloalkyl of C_{3-8}, or aralkyl of C_{7-12} including pharmaceutically acceptable salts thereof in unit dosage form of 50 to 500 mg. with pharmaceutical carrier for oral and parenteral administration and process for therapeutic or prophylactic treatment of humans and animals hosting a lincomycin-susceptible parasite.

CROSS REFERENCE TO RELATED APPLICATIONS

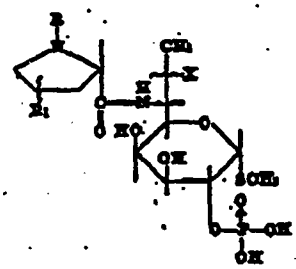
This application is a continuation-in-part of application Ser. No. 602,116, filed Dec. 16, 1966.

BRIEF SUMMARY OF INVENTION

This invention relates to lincomycin and clindamycin-2-phosphates and compounds related thereto (compounds of the Formula 1) and pharmaceutically acceptable salts thereof prepared in unit dosage form of from 50 to 500 mg. in association with a pharmaceutical carrier and a process for prophylactic and therapeutic treatment of humans and animals hosting a lincomycin-susceptible parasite.

DETAILED DESCRIPTION

This application relates to novel compositions and process of treatment and more particularly to compositions comprising, in unit dosage form, a compound of the formula



Formula 1

wherein X is hydroxy, chlorine, or bromine, R_1 is alkyl of from 1 to 8 carbon atoms, cycloalkyl of from 3 to 8 carbon

atoms or aralkyl of from 7 to 12 carbon atoms and R_2 is hydrogen, alkyl of from 1 to 8 carbon atoms, cycloalkyl of from 3 to 8 carbon atoms or aralkyl of from 7 to 12 carbon atoms; and including the pharmaceutically acceptable salts thereof in combination with a pharmaceutical carrier.

Typical, but not all, therapeutic compounds of this invention include the following as referred to the above Formula 1:

R_1	R_2	X
Trans n-propyl	Methyl	(R)-OH
Do	Hydrogen	Do.
Do	Ethyl	Do.
Do	Isopropyl	Do.
Do	n-Butyl	Do.
Do	Cyclohexyl	Do.
n-Pentyl	Methyl	Do.
Do	Hydrogen	Do.
Do	n-Butyl	Do.
N-hexyl	Methyl	Do.
Do	Hydrogen	Do.
Do	n-Butyl	Do.
trans n-propyl	Methyl	(S)-Cl
Do	Hydrogen	Do.
Do	Ethyl	Do.
Do	Isopropyl	Do.
Do	n-Butyl	Do.
Do	Cyclohexyl	Do.
n-Pentyl	Methyl	Do.
Do	Hydrogen	Do.
Do	n-Butyl	Do.
Trans n-propyl	Methyl	(S)-Br
n-Pentyl	Hydrogen	Do.

In the above Formula 1, the vertical wavy line ∫ is used to indicate that the group R_1 can be in position cis (below the plane of the ring) or trans (above the plane of the ring), with respect to the carbonyl group. The horizontal wavy line ~ is used to indicate that both epimers are to be included, i.e., the D-erythro configuration and L-threo configuration are intended.

Examples of alkyl are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl and isomeric forms thereof. Examples of cycloalkyl are cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 2-methylcyclopentyl, 2,3-dimethylcyclobutyl, 4-methylcyclohexyl, and 3-cyclopentylpropyl. Examples of aralkyl are benzyl, phenethyl, α-phenylpropyl, and α-naphthylmethyl.

The compounds of the Formula 1 can be prepared by the methods disclosed in copending application Ser. No. 602,116 filed Dec. 16, 1966.

Further, the invention relates to a process for therapeutic treatment of humans and animals hosting bacterial and other microparasites and the prophylactic treatment of a disease-susceptible host comprising the administration of a compound of the formula 1 or a pharmaceutically acceptable salt thereof to the host.

The compounds of the invention have essentially the same antibacterial spectrum in vivo as the antibiotic lincomycin and can be used for the same purposes as lincomycin. The compounds of the invention are particularly useful for oral administration to animals, including birds, because they lack the bitter taste of lincomycin.

The compositions of the present invention are presented for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of a compound of Formula 1 or its pharmacologically acceptable salts.

For oral administration either solid or fluid unit dosage forms can be prepared. For preparing solid compositions such as tablets, the principal active ingredient is mixed with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methylcellulose, and functionally similar materials as pharmaceutical diluents or carriers. The tablets can be laminated or

otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or predetermined successive action of the enclosed medication. For example, the tablet can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former.

Alternatively, the two component system can be utilized for preparing tablets containing two or more incompatible active ingredients. Wafers are prepared in the same manner as tablets, differing only in shape and the inclusion of sucrose or other sweetener and flavor. In their simplest embodiment, capsules, like tablets, are prepared by mixing the antibiotic with an inert pharmaceutical diluent and filling the mixture into a hard gelatin capsule of appropriate size. In another embodiment, capsules are prepared by filling hard gelatin capsules with polyacrylic acid coated beads containing the antibiotic. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the antibiotic with an acceptable vegetable oil, light liquid petrolatum or other inert oil.

Fluid unit dosage forms for oral administration such as syrups, elixirs, and suspensions can be prepared. The water-soluble forms can be dissolved in an aqueous vehicle together with sugar, aromatic flavoring agents and preservatives to form a syrup. An elixir is prepared by using a hydro-alcoholic (ethanol) vehicle with suitable sweeteners such as sugar and saccharin, together with an aromatic flavoring agent.

Suspensions can be prepared of the insoluble forms with a syrup vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

Topical ointments can be prepared by dispersing the antibiotic in a suitable ointment base such as petrolatum, lanolin, polyethylene glycols, mixtures thereof, and the like. Advantageously, the antibiotic is finely divided by means of a colloid mill utilizing light liquid petrolatum as a levigating agent prior to dispersing in the ointment base. Topical creams and lotions are prepared by dispersing the antibiotic in the oil phase prior to the emulsification of the oil phase in water.

For parenteral administration, fluid unit dosage forms are prepared utilizing the antibiotic and a sterile vehicle, water being preferred. The antibiotic, depending on the form and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the water-soluble antibiotic can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampule and sealing. Advantageously, adjuvants such as local anesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection is supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the antibiotic is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The antibiotic can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the antibiotic.

The term unit dosage form as used in the specification and claims refers to physically discrete units suitable as unitary dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specifications for the novel unit dosage forms of this invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for therapeutic use in humans and animals, as disclosed in detail in this specification, these being features of the present invention. Examples of suitable unit dosage forms in accord with this invention are tablets, capsules, pills, troches, suppositories, powder packets, granules, wafers, cachets, teaspoonfuls, tablespoonfuls, dropperfuls, ampules, vials, segregated multiples of any of the foregoing, and other forms as herein described.

In addition to the administration of a compound of Formula 1 as the principal active ingredient of compositions for the treatment of the conditions described herein, the said compound can be included with other types of compounds to obtain advantageous combinations of properties. Such combinations include a compound of Formula 1 with antibiotics such as spectinomycin, chloramphenicol, tetracyclines(e.g., tetracycline, oxytetracycline and chlortetracycline), penicillin, erythromycin, novobiocin, kanamycin, streptomycin, neomycin, polymyxin, bacitracin, nystatin, and endomycin to broaden the bacterial spectrum of the composition and for synergistic action against particular bacteria; steroids having antiinflammatory activity such as hydrocortisone, prednisolone, methylprednisolone, fluprednisolone and the like; analgetics such as aspirin, sodium salicylate, (acetylsallcylic acid) anhydride, acetaminophen and salicylamide; antihistamines, such as chlorpheniramine maleate, diphenhydramine, promethazine, pyrathiazine, and the like; sulfas, such as sulfadiazine, sulfamethazine, sulfamerazine, sulfacetamide, sulfadimethoxazole, sulfamethiazole, and the like, antifungals, such as undecylenic acid, sodium propionate, salicylanilide, sodium caprylate, and benzthidine; and the vitamins.

The dosage of a compound of Formula 1 for treatment depends on route of administration, the age, weight, and condition of the patient; and the particular disease to be treated. A dosage schedule of from about 50 to 500 mg., 1 to 4 times daily (every six hours), embraces the effective range for the treatment of most conditions for which the compositions are effective. For children the dosage is calculated on the basis of 6 to 8 mg./kg. by weight to be administered every six hours.

The antibiotic is compounded with a suitable pharmaceutical carrier in unit dosage form for convenient and effective administration. In the preferred embodiments of this invention, the dosage units contain a compound of Formula 1 in: 50, 100, 200 and 500 mg. amounts for systemic treatment; in 0.25, 0.5, 1, 2 and 5% amounts for topical or localized treatment; and 5 to 25% w./v. for parenteral treatment. The dosage of compositions containing a compound of Formula 1 and one or more other active ingredients is to be determined with reference to the usual dosage of each such ingredient.

The following examples are illustrative of the best mode contemplated by the inventors for carrying out their invention and are not to be construed as limiting.

EXAMPLE 1

Capsules

One thousand two-piece hard gelatin capsules for oral use, each containing 200 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of materials:

	Gm.
Lincomycin-2-phosphate	200
Corn starch	150
Talc	75
Magnesium stearate	2.5

The materials are thoroughly mixed and then encapsulated in the usual manner.

The foregoing capsules are useful for the systemic treatment of infection in adult humans by the oral administration of 1 capsule every 4 hours.

Using the procedure above, capsules are similarly prepared containing lincomycin-2-phosphate in 50, 100, and

500 mg. amounts by substituting 50, 100 and 500 gm. of lincomycin-2-phosphate for the 200 gm. used above.

EXAMPLE 2

Capsules

One thousand two-piece hard gelatin capsules for oral use, each containing 200 mg. of lincomycin-2-phosphate and 250 mg. of tetracycline hydrochloride, are prepared from the following types and amounts of ingredients:

	Gm.
Lincomycin-2-phosphate	200
Tetracycline hydrochloride	250
Talc	75
Magnesium stearate	2.5

The ingredients are thoroughly mixed and then encapsulated in the usual manner.

The foregoing capsules are useful for the systemic treatment of infection in adult humans by the oral administration of 1 capsule every 6 hours.

Using the procedure above, capsules are similarly prepared containing lincomycin-2-phosphate and each of the following antibiotics in place of tetracycline by substituting 250 gm. of such other antibiotic for tetracycline: chloramphenicol, oxytetracycline, chlortetracycline, fumagillin, erythromycin, streptomycin, dihydrostreptomycin and novobiocin. When a penicillin, such as potassium penicillin G, is to be used in place of tetracycline, 250,000 units per capsule is employed.

Such combination products are useful for the systemic treatment of mixed infections in adult humans by the oral administration of 1 capsule every 6 hours.

EXAMPLE 3

Tablets

One thousand tablets for oral use, each containing 500 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of materials:

	Gm.
Lincomycin-2-phosphate	500
Lactose	125
Corn starch	65
Magnesium stearate	7.5
Light liquid petrolatum	3

The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets, each tablet containing 500 mg. of lincomycin-2-phosphate.

The foregoing tablets are useful for systemic treatment of infections in adult humans by oral administration of 1 tablet every 4 hours.

Using the above procedure, except for reducing the amount of lincomycin-2-phosphate to 200 gm., tablets containing 200 mg. of lincomycin-2-phosphate are prepared.

EXAMPLE 4

Tablets

One thousand oral tablets, each containing 100 mg. of lincomycin-2-phosphate and a total of 250 mg. (83.3 mg. each) of sulfadiazine, sulfamerazine, and sulfamethazine, are prepared from the following types and amounts of materials:

	Gm.
Lincomycin-2-phosphate	200
Sulfadiazine	83.3
Sulfamerazine	83.3
Sulfamethazine	83.3
Lactose	50
Corn starch	50
Calcium stearate	5.5
Light liquid petrolatum	5

The ingredients are thoroughly sifted and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets, each containing 200 mg. of lincomycin-2-phosphate and a total of 250 mg. (83.3 mg. each) of sulfadiazine, sulfamerazine, and sulfamethazine.

The foregoing tablets are useful for systemic treatment of infections by the oral administration of 4 tablets first and then 1 every six hours.

For the treatment of urinary infections, the triple sulfas in the above formulation is advantageously replaced by 250 gm. of sulfamethylthiadiazole or 250 gm. of sulfacetamide.

EXAMPLE 5

Granules

2367 gm. of a granulation suitable for reconstitution with water prior to use is prepared from the following types and amounts of ingredients:

	Gm.
Lincomycin-2-phosphate	150
Tetracycline hydrochloride	150
Lecithin	5
Sucrose, powdered	2000
Flavor	60
Sodium metabisulfite	2

The tetracycline is finely divided and coated with the lecithin. The coated tetracycline, lincomycin-2-phosphate, sugar, flavor, and sodium metabisulfite are mixed together until thoroughly blended. The powder mixture is wetted with water and forced through a screen to form granules. The granules are dried and 23.67 gm. filled into 60 cc. bottles. Prior to use sufficient water is added to the granules to make 60 cc. of composition.

The foregoing composition is useful for systemic treatment of infection, particularly in children at a dose of one teaspoonful 4 times daily.

EXAMPLE 6

Oral syrup

One thousand cc. of an aqueous suspension for oral use, containing in each 5 cc. dose, one-half gram of total sulfas and 200 mg. of lincomycin-2-phosphate is prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate—40 gm.
Sulfadiazine—33.3 gm.
Sulfamerazine—33.3 gm.
Sulfamethazine—33.3 gm.
Citric acid—2 gm.
Benzoic acid—1 gm.
Sucrose—700 gm.
Tragacanth—5 gm.
Lemon oil—2 cc.
Deionized water, q.s.—1000 cc.

The citric acid, benzoic acid, sucrose, tragacanth, and lemon oil are dispersed in sufficient water to make 850 cc. of solution. The lincomycin-2-phosphate and finely powdered sulfas are stirred into the syrup until uniformly distributed. Sufficient water is added to make 1000 cc.

The composition so prepared is useful in the systemic treatment of pneumonia in adult humans at a dose of 1 teaspoonful 4 times a day.

EXAMPLE 7

Parenteral solution

A sterile aqueous solution for intramuscular use, containing in 1 cc. 75 mg. of lincomycin-2-phosphate is prepared from the following types and amounts of materials:

Lincomycin-2-phosphate—75 gm.
Lidocaine hydrochloride—4 gm.
Methylparaben—2.5 gm.
Propylparaben—0.17 gm.
Water for injection, q.s.—1000 cc.

The ingredients are dissolved in the water and the solution sterilized by filtration. The sterile solution is filled into vials and the vials sealed.

EXAMPLE 8

Parenteral solution

A sterile aqueous solution for intramuscular use, containing in 1 cc. 250 mg. of lincomycin-2-phosphate, as the Na salt is prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate—250 gm.
Sodium hydroxide 10% solution, q.s.
Water for injection, q.s.—1000 cc.

The lincomycin-2-phosphate is added to the water and sufficient sodium hydroxide added to form a solution and the solution sterilized by filtration. The sterile solution, in the amount of 2 cc., is aseptically filled into sterile vials and frozen. The water is removed under high vacuum and the vials containing the lyophilized powder are sealed. Just prior to use, sufficient sterile water for injection to make 2 cc. of solution is added to the vial.

EXAMPLE 9

Topical ointment

One thousand gm. of 0.25% ointment is prepared from the following types and amounts of ingredients:

	Gm.
Lincomycin-2-phosphate	2.5
Zinc oxide	50
Calamine	50
Liquid petrolatum (heavy)	250
Wool fat	200
White petrolatum, q.s.	1000

The white petrolatum and wool fat are melted and 00 gm. of liquid petrolatum added thereto. The lincomycin-2-phosphate, zinc oxide and calamine are added the remaining liquid petrolatum and the mixture milled until the powders are finely divided and uniformly dispersed. The powder mixture is stirred into the white petrolatum mixture and stirring continued until the ointment congeals.

The foregoing ointment is usefully applied topically the skin of mammals for the treatment of infection.

The foregoing composition can be prepared by omitting the zinc oxide and calamine.

Following the procedure above, ointments are similarly prepared containing lincomycin-2-phosphate in 0.5, 1, 2 and 5% amounts by substituting 5, 10, 20, and 50 gm. of lincomycin-2-phosphate for the 2.5 gm. used above.

EXAMPLE 10

Cream

One thousand gm. of a vaginal cream are prepared from the following types and amounts of ingredients:

	Gm.
Lincomycin-2-phosphate	50
Tegacid Regular [1]	150
Spermaceti	100
Propylene glycol	50
Polysorbate 80	5
Methylparaben	1
Deionized water, q.s.	1000

[1] Self-emulsifying glyceryl monostearate from Goldschmidt Chemical Corporation, New York, N.Y.

The Tegacid and spermaceti are melted together at a temperature of 70–80° C. The methylparaben is dissolved in about 500 gm. of water and the propylene glycol, polysorbate 80, and lincomycin-2-phosphate are added in turn, maintaining a temperature of 75–80° C. The methylparaben mixture is added slowly to the Tegacid and spermaceti melt, with constant stirring. The addition is continued for at least 30 minutes with continued stirring until the temperature has dropped to 40–45° C. The pH of the final cream is adjusted to 3.5 by incorporation 2.5 gm. of citric acid and 0.2 gm. of dibasic sodium phosphate dissolved in about 50 gm. of water. Finally, sufficient water is added to bring the final weight to 1000 gm. and the preparation stirred to maintain homogeneity until cooled and congealed.

The foregoing composition is useful for the treatment of vaginal infections in humans.

EXAMPLE 11

Ointment, ophthalmic

One thousand gm. of an ophthalmic ointment containing 0.5% lincomycin-2-phosphate are prepared from the following types and amounts of ingredients:

	Gm.
Lincomycin-2-phosphate	5
Bacitracin	12.2
Polymyxin B sulfate (10,000 units/mg.)	1
Light liquid petrolatum	250
Wool fat	200
White petrolatum, q.s.	1000

The antibiotics are finely divided by means of an air micronizer and added to the light liquid petrolatum. The mixture is passed through a colloid mill to uniformly distribute the antibiotics. The wool fat and white petrolatum are melted together, strained, and the temperature adjusted to 45–50° C. The liquid petrolatum slurry is added and the ointment stirred until congealed. Suitably, the ointment is packaged in one dram ophthalmic tubes.

The foregoing ointment is usefully applied to the eye for treatment of localized infection in humans and other animals.

Advantageously, the foregoing composition can contain 5 gm. (0.5%) of methylprednisolone for the treatment of inflammation, and, alternatively, the bacitracin and polymyxin B sulfate can be omitted.

EXAMPLE 12

Eye-ear drops

One thousand cc. of a sterile aqueous solution for eye or ear use containing 10 mg. of lincomycin-2-phosphate and 10 mg. of prednisolone succinate sodium in each cc. is prepared from the following types and amounts of ingredients:

Lincomycin-2-phosphate—10 gm.
Prednisolone succinate sodium—10 gm.
Sodium citrate—4.5 gm.
Polyethylene glycol 4000—120 gm.
Myristyl-γ-picolinium chloride—0.2 gm.
Polyvinylpyrrolidone—1 gm.
Deionized water, q.s. ad—1000 cc.

The ingredients are dissolved in the water and the resulting solution is sterilized by filtration. The solution is aseptically filled into sterile dropper containers.

The composition so prepared is useful in the topical treatment of inflammation and infection of the eye and ear as well as other sensitive tissues of the animal body.

EXAMPLE 13

Troches

Ten thousand troches are prepared from the following types and amounts of ingredients:

	Gm.
Lincomycin-2-phosphate	100
Neomycin sulfate	50
Polymyxin B sulfate (10,000 units/mg.)	1
Ethyl aminobenzoate	50
Calcium stearate	150
Powdered sucrose, q.s.	5000

The powdered materials are mixed thoroughly and then compressed into half gram troches following the usual techniques for the preparation of compressed tablets.

The troches are held in the mouth and allowed to dissolve slowly to provide treatment for the mouth and throat.

EXAMPLE 14

Suppository, rectal

One thousand suppositories, each weighing 2.5 gm. and containing 100 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of ingredients:

	Gm.
Lincomycin-2-phosphate	100
Polymyxin B sulfate (10,000 units/mg.)	1.25
6α-methylprednisolone	1
Ethyl aminobenzoate	75
Zinc oxide	62.5
Propylene glycol	162.5
Polyethylene glycol 4000, q.s.	2500

The lincomycin-2-phosphate, polymyxin B sulfate, 6-methylprednisolone, ethyl aminobenzoate, and zinc oxide are added to the propylene glycol and the mixture milled until the powders are finely divided and uniformly dispersed. The polyethylene glycol 4000 is melted and the propylene glycol dispersion added slowly with stirring. The suspension is poured into unchilled molds at 40° C. The composition is allowed to cool and solidify and then removed from the mold and each suppository foil wrapped.

The foregoing suppositories are inserted rectally for local treatment of inflammation and infection.

Alternatively, the foregoing composition can be prepared omitting the steroid.

EXAMPLE 15

Mastitis ointment

One thousand gm. of an ointment for the treatment of mastitis in dairy cattle is prepared from the following types and amounts of ingredients:

	Gm.
Lincomycin-2-phosphate	50
Prednisolone acetate	0.5
Light liquid petrolatum	300
Chlorobutanol, anhydrous	5
Polysorbate 80	5
2% aluminum monostearate-peanut oil gel	400
White petrolatum, q.s.	1000

The lincomycin-2-phosphate and prednisolone acetate are milled with the light liquid petrolatum until finely divided and uniformly dispersed. The chlorobutanol, polysorbate 80, peanut oil gel and white petrolatum are heated to 120° F. to form a melt and the liquid petrolatum dispersion stirred in. With continued stirring the dispersion is allowed to cool (and congeal) to room temperature and is filled into disposable mastitis syringes in 10 gm. doses.

EXAMPLE 16

Animal feed

One thousand gm. of a feed mix is prepared from the following types and amounts of ingredients:

	Gm.
Lincomycin-2-phosphate	10
Soybean meal	400
Fish meal	400
Wheat germ oil	50
Sorghum molasses	140

The ingredients are mixed together and pressed into pellets.

The composition can be fed to laboratory animals, i.e., rats, mice, guinea pigs, and rabbits for prophylaxis during shipping.

For larger animals, the composition can be added to the animal's regular feed in an amount calculated to give the desired dose of lincomycin-2-phosphate.

EXAMPLE 17

Following the procedure of each of the preceding Examples 1 and 3, each member selected from the group consisting of sodium novobiocin, calcium novobiocin, chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline, tetracycline hydrochloride, and tetracycline phosphate complex is added in 50, 100, and 250 gm. amounts to provide a combination having a wider spectrum of therapeutic effectiveness in the treatment of infectious diseases resulting from mixed organisms susceptible to lincomycin-2-phosphate as indicated in the present specification and the above indicated antibiotics as already well known to the medical art.

EXAMPLE 18

Following the procedure of the preceding Examples 1 through 16, inclusive, each member selected from the group consisting of

lincomycin-2-phosphate,
hemiammonium salt,
7(S)-chloro-7-deoxylincomycin-2-phosphate,
7(S)-chloro-7-deoxy-1'-dimethyllincomycin-2-phosphate,
7(S)-chloro-7-deoxy-4'-depropyl-4'-pentyl-1'-demethyllincomycin-2-phosphate,
7(S)-chloro-7-deoxy-4'-depropyl-4'-pentyl-1'-demethyllincomycin-2-phosphate,
calcium salt,
or 7(S)-chloro-7-deoxy-4'-depropyl-4'-pentyl-1'-demethyllincomycin-2-phosphate,

magnesium salt is substituted in an equivalent amount for the lincomycin-2-phosphate shown in the example to provide similar therapeutic properties.

EXAMPLE 19

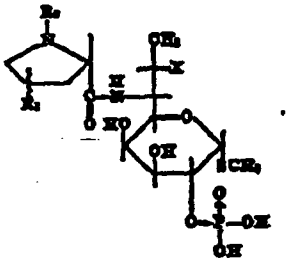
Following the procedure of the preceding Examples 1 through 5, 9 through 11, and 13 through 16, inclusive, each member selected from the group consisting of

7(S)-chloro-7-deoxylincomycin-2-phosphate,
calcium salt,
7(S)-chloro-7-deoxylincomycin-2-phosphate,
magnesium salt,
7(S)-chloro-7-deoxy-1'-demethyllincomycin-2-phosphate,
calcium salt,
or 7(S)-chloro-7-deoxy-1'-demethyllincomycin-2-phosphate,

magnesium salt is substituted in an equivalent amount for the lincomycin-2-phosphate shown in the example and provides similar therapeutic properties.

What is claimed is:

1. An antibacterial composition comprising, in unit dosage form, from about 50 to 500 mg. of a compound of the formula:



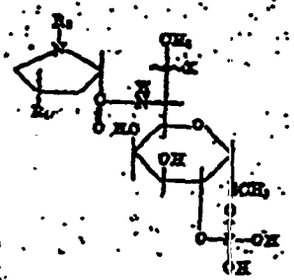
wherein X is hydroxy, chlorine or bromine, R_1 is alkyl of C_{1-4}, cycloalkyl or C_{3-5}, or aralkyl of C_{7-10} and R_2

hydrogen, alkyl of C_{1-8}, cycloalkyl of C_{3-8}, or aralkyl of C_{7-12}, or pharmaceutically acceptable salts thereof, as an essential active ingredient, in combination with a pharmaceutical carrier.

2. A composition of claim 1 wherein the concentration of the compound of the formula is from about 0.25% w./w. to about 25% w./w.

3. A composition of claim 1 wherein the concentration of the compound of the formula is from about 5% w./w. to about 25% w./w. and wherein the pharmaceutical carrier is a sterile vehicle for parenteral administration.

4. A process for treating a bacterial disease in humans and animals which comprises administering to the bacterial host an antibacterial therapeutic amount of a compound of the formula:

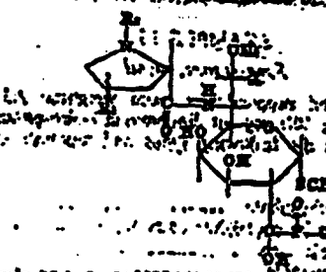


wherein X is hydroxy, chlorine or bromine, R_1 is alkyl of C_{1-6}, cycloalkyl of C_{3-6} or aralkyl of C_{7-12}, R_2 is hydrogen, alkyl of C_{1-6}, cycloalkyl of C_{3-6} or aralkyl of C_{7-12} or pharmaceutically acceptable salts thereof in combination with a pharmaceutical carrier.

5. A process according to claim 4 wherein the compound of the formula is administered in unit dosage form

in an amount of from about 50 to about 500 mg. of said compound in association with a pharmaceutical carrier.

6. A process of prophylactic treatment for the prevention of a bacterial disease comprising the administering to a disease-susceptible human or animal host a prophylactic antibacterial amount of a compound of the formula:



wherein X is hydroxy, chlorine or bromine, R_1 is alkyl of C_{1-6}, cycloalkyl of C_{3-6} or aralkyl of C_{7-12}, R_2 is hydrogen, alkyl of C_{1-6}, cycloalkyl of C_{3-6} or aralkyl of C_{7-12} or pharmaceutically acceptable salts thereof in combination with a pharmaceutical carrier.

7. A process according to claim 6 wherein the compound of the formula is administered in unit dosage form in an amount of from about 50 to about 500 mg. of said compound in association with a pharmaceutical carrier.

References Cited

UNITED STATES PATENTS

3,150,042 9/1964 Moss et al. ..... 424—274
3,268,556 8/1966 Hoeksema ..... 424—274

ALBERT T. MEYERS, Primary Examiner

J. D. GOLDBERG, Assistant Examiner

VOLUME III

Approved Drug Products and Legal Requirements

APPEARS THIS WAY
ON ORIGINAL

USP DI®

1998

18TH EDITION

BEST POSSIBLE COPY

text printed on recycled paper

By authority of the United States Pharmacopeial Convention, Inc.

017

CLINDAMYCIN HYDROCHLORIDE

CAPSULE; ORAL

CLEOCIN HCL

AB	+	PHARMACIA AND UPJOHN	EQ 75MG BASE	N050162 001
AB	+		EQ 150MG BASE	N050162 002
	+		EQ 300MG BASE	N050162 003 APR 14, 1988

CLINDAMYCIN HCL

AB		DANBURY PHARMA	EQ 75MG BASE	N063082 001 JUL 31, 1991
AB			EQ 150MG BASE	N063083 001 JUL 31, 1991
AB		TEVA	EQ 75MG BASE	N063027 001 SEP 20, 1989
AB			EQ 150MG BASE	N063029 001 SEP 20, 1989

CLINDAMYCIN PALMITATE HYDROCHLORIDE

POWDER FOR RECONSTITUTION; ORAL

CLEOCIN

		PHARMACIA AND UPJOHN	EQ 75MG BASE/5ML	N062644 001 APR 07, 1986

CLINDAMYCIN PHOSPHATE

CREAM; VAGINAL

CLEOCIN

	+	PHARMACIA AND UPJOHN	EQ 2% BASE	N050680 001 AUG 11, 1992

GEL; TOPICAL

CLEOCIN T

	+	PHARMACIA AND UPJOHN	EQ 1% BASE	N050615 001 JAN 07, 1987

INJECTABLE; INJECTION

CLEOCIN PHOSPHATE

AP	+	PHARMACIA AND UPJOHN	EQ 150MG BASE/ML	N050441 001
AP			EQ 150MG BASE/ML	N062803 001 OCT 16, 1987

CLEOCIN PHOSPHATE IN DEXTROSE 5% IN PLASTIC CONTAINER

AP	+	PHARMACIA AND UPJOHN	EQ 6MG BASE/ML	N050639 001 AUG 30, 1989
AP	+		EQ 12MG BASE/ML	N050639 002 AUG 30, 1989
	+		EQ 18MG BASE/ML	N050639 003 APR 10, 1991

CLINDAMYCIN PHOSPHATE *(continued)*

INJECTABLE; INJECTION

CLINDAMYCIN PHOSPHATE

AP		ABBOTT	EQ 150MG BASE/ML	N062800 001 JUL 24, 1987
AP			EQ 150MG BASE/ML	N062801 001 JUL 24, 1987
AP			EQ 150MG BASE/ML	N062943 001 SEP 29, 1988
AP		ASTRA	EQ 150MG BASE/ML	N062928 001 FEB 13, 1989
AP		BEDFORD	EQ 150MG BASE/ML	N063163 001 JUN 30, 1994
AP		ELKINS SINN	EQ 150MG BASE/ML	N062806 001 OCT 15, 1987
AP			EQ 150MG BASE/ML	N062953 001 APR 21, 1988
AP		GENSIA	EQ 150MG BASE/ML	N063041 001 DEC 29, 1989
AP			EQ 150MG BASE/ML	N063282 001 MAY 29, 1992
AP		LEDERLE	EQ 150MG BASE/ML	N062889 001 APR 25, 1988
AP			EQ 150MG BASE/ML	N063068 001 AUG 28, 1989
AP		LOCH	EQ 150MG BASE/ML	N062905 001 MAY 09, 1988
AP		MARSAM	EQ 150MG BASE/ML	N062913 001 OCT 20, 1988
AP		SOLOPAK	EQ 150MG BASE/ML	N062819 001 MAR 15, 1988
AP			EQ 150MG BASE/ML	N062852 001 MAR 17, 1988
AP		STERIS	EQ 150MG BASE/ML	N062900 001 JUN 08, 1988
AP			EQ 150MG BASE/ML	N063079 001 MAR 05, 1990

CLINDAMYCIN PHOSPHATE IN DEXTROSE 5%

AP	+	FUJISAWA	EQ 900MG BASE/100ML	N050635 001 DEC 22, 1989

CLINDAMYCIN PHOSPHATE IN DEXTROSE 5% IN PLASTIC CONTAINER

AP	+	BAXTER HLTHCARE	EQ 6MG BASE/ML	N050648 001 DEC 29, 1989
AP	+		EQ 12MG BASE/ML	N050648 002 DEC 29, 1989
AP	+		EQ 900MG BASE/100ML	N050648 003 DEC 29, 1989

LOTION; TOPICAL

CLEOCIN T

	+	PHARMACIA AND UPJOHN	EQ 1% BASE	N050600 001 MAY 31, 1989

505(b)(2) CERTIFICATION

As per 21 CFR 314.54(a)(1)(iv) Clindagel, LLC certifies that this 505(b)(2) application is for a new indication (dosing regimen) of Clindagel™ (clindamycin phosphate gel) in the treatment of acne vulgaris. Clindagel is indicated for a once a day treatment of acne vulgaris while Cleocin-T gel (1% clindamycin phosphate), the listed product, is indicated for twice a day use for the treatment of acne vulgaris.

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs
Target Research Associates, Inc.

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Summary from FDA

11-20-00

NOV 20

EXCLUSIVITY SUMMARY for NDA # 50-782 SUPPL # _____

Trade Name: Tradename Generic Name: clindamycin phosphate, [redacted] gel, 1%
Applicant Name: Clindagel LLC, (Target Research Associates) HFD- 540
Approval Date: 11-21-00

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/
   If yes, what type (SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")
   YES /___/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   d) Did the applicant request exclusivity? YES /_X_/ NO /___/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
   3 Years

   e) Has pediatric exclusivity been granted for this Active Moiety? YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

APPEARS THIS WAY
ON ORIGINAL

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety. YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# **50-441** (Cleocin Phosphate Solution),
NDA# **50-537** (Cleocin Topical Solution)
NDA# **50-600** (Cleocin T Topical Solution)
NDA# **50-615** (Cleocin T Gel)
NDA# **50-635** & **50-636** (Clindamycin Phosphate 5% Injection)
NDA# **50-639** (Cleocin Phosphate IV Solution)
NDA# **50-648** (Clindamycin Phosphate Injection)
NDA# **50-680** (Cleocin Vaginal Cream)
NDA# **50-767** (Cleocin Vaginal Cream OV)

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_**X**_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_**X**_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/ **N/A**

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # CGEL-003

Investigation #2, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # **CGEL-003**

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # **56,487** YES /_X_/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? **N/A**

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

/S/

Signature of Preparer/Indira Kumar/RPM — Date 11/20/00

/S/

Jonathan K. Wilkin, M.D./Division Director — Date 11/20/00

PATENT AND EXCLUSIVITY INFORMATION

The sponsor, Clindagel, LLC, seeks marketing approval of Clindagel™ (— clindamycin phosphate — gel) in the treatment of acne vulgaris via a 505(b)(2) application. Clindagel™ is similar in composition to the listed drug Cleocin-T gel (1% clindamycin phosphate) which is approved for twice a day treatment of acne vulgaris.

There is currently no patent protection for Clindagel™ (— clindamycin phosphate — gel), which is the subject of this 505(b)(2) application. Persuant to 21CFR 314.108 Clindagel™ qualifies for 3 years of exclusivity since a clinical investigation was essential in showing effectiveness of Clindagel™ in a once a day application for the treatment of acne vulgaris and the clinical investigation was conducted by the sponsor (as per IND # 56,487).

Upjohn's patent for clindamycin phosphate has expired and additionally, as listed in the Orange Book, Cleocin-T gel has no additional exclusivity. Information on Upjohn's Patent 3,509,256 issued April 28, 1970 covering clindamycin phosphate and information on Cleocin-T gel from the Orange Book can be found on the following pages.

To the best of Clindagel, LLC's knowledge, Clindagel™ (— clindamycin phosphate — gel) does not infringe on any patents covering clindamycin phosphate or products containing clindamycin phosphate.

APPEARS THIS WAY
ON ORIGINAL

Clindagel, LLC
4189 Chaparral Court • Santa Rosa, CA 95409
Phone: (707) 483-7489 • Fax: (707) 546-3058

Clindagel, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Gordon Dow, Pharm.D.
Clindagel, LLC

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attached	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Gordon J. Dow	Manager
FIRM/ORGANIZATION: Clindagel, LLC	
SIGNATURE: Gordon J. Dow	DATE: 1-6-00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Clindagel™ Clinical Investigators

Investigator	Clinical Study
	CGEL-001, CGEL-002
[redacted]	CGEL-001, CGEL-002
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003
[redacted]	CGEL-003, CGEL-005
[redacted]	CGEL-005

APPEARS THIS WAY
ON ORIGINAL

TARGET RESEARCH ASSOCIATES
CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

November 22, 2000

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
9201 Corporate Boulevard
North 214
Rockville, MD 20850

RE: **NDA 50-782**
Clindagel, LLC, Santa Rosa, CA
Clindagel™ (Clindamycin Phosphate [redacted] gel), 1%
Indication: Once a day treatment of acne vulgaris
Response to the November 9 FDA request for formulation, specifications and acceptance criteria of the [redacted]

Dear Dr. Wilkin:

Reference is made to NDA 50-782 for Clindagel™(Clindamycin Phosphate [redacted] gel) 1% for the once a day treatment of acne vulgaris submitted to FDA on January 27, 2000.

On behalf of Clindagel, LLC, we are hereby submitting in duplicate the following information in response to the November 9 request by the agency. The FDA request is listed below in boldface type followed by the applicable response.

1. **[redacted], a Type I, erroneously listed as a Type III in the submission, does not contain the information required for the [redacted], the DMF holder, has informed the agency that a formulation disclosure statement (formulation, specifications and acceptance criteria) is provided to their clients with every lot tney supply to their clients and that the formulation disclosure statement of their product could be provided to the agency by the applicant. Please provide the formulation, specifications and acceptance criteria of the [redacted]**

Clindagel, LLC has received the formulation, specifications and acceptance criteria for the [redacted] as requested, and is providing this information in the following attachment.

554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

Please let me know if you have any questions regarding the contents of this submission.

Sincerely,

Jill A. Powers, RAC
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

(T)

Number of Pages Redacted 11

❖❖❖

Confidential,
Commercial Information

(T)

(U)

Number of Pages Redacted 2

❖❖❖

Confidential,
Commercial Information

(U)

TARGET RESEARCH ASSOCIATES
CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

November 21, 2000

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
9201 Corporate Boulevard
North 214
Rockville, MD 20850

APPEARS THIS WAY
ON ORIGINAL

RE: NDA 50-782
Clindagel, LLC, Santa Rosa, CA
Clindagel™ (Clindamycin Phosphate [redacted] gel), 1%
Indication: Once a day treatment of acne vulgaris
Submission of mock up container and carton labels

Dear Dr. Wilkin:

Reference is made to NDA 50-782 for Clindagel™(Clindamycin Phosphate [redacted] gel) 1% for the once a day treatment of acne vulgaris submitted to FDA on January 27, 2000

Please be advised the Clindagel, LLC does not intend to market Clindagel but will [redacted]. In addition, the mock up does not include the revised storage statement requested by the agency in the fax of November 9, 2000. Once an agreement has been made on the label copy between the agency and Clindagel, LLC, the final label copy containing the name of the marketing company and the revised storage statement will be submitted.

Please let me know if you have any questions regarding the contents of this submission.

Sincerely,

Jill A. Powers, RAC
Manager, Regulatory Affairs

(V)

Number of Pages Redacted 6

❖❖❖

Draft Labeling
(not releasable,

(V)

TARGET RESEARCH ASSOCIATES
CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

November 15, 2000

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
9201 Corporate Boulevard
North 214
Rockville, MD 20850

RE: NDA 50-782
Clindagel, LLC, Santa Rosa, CA
Clindagel™ (Clindamycin Phosphate ——— gel), 1%
Indication: Once a day treatment of acne vulgaris
120 Day Safety Update Information

Dear Dr. Wilkin:

Reference is made to NDA 50-782 for Clindagel™(Clindamycin Phosphate ——— gel) 1% for the once a day treatment of acne vulgaris submitted to FDA on January 27, 2000.

On behalf of Clindagel, LLC, we are hereby submitting in duplicate a confirmation by Clindagel, LLC that all clinical studies are complete and all safety data were reported in either the original NDA application or the NDA amendment filed on April 27, 2000. Therefore, pursuant to 21 CFR 314.50(d)(5)(vi)(b) there is no new safety information to report.

Please let me know if you have any questions regarding the contents of this submission.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Jill A. Powers, RAC
Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-400 OPDRA, Attn:Sammie Beam /Patrick Guinn

FROM: HFD-540 (Division of Dermatologic and Dental Drug Products) Jonathan Wilkin/Division Director

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
ember 13, 2000		50-782	Submission of New Proprietary Name	January 27, 2000

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Clindagel (clindamycin phosphate) 1% Topical Gel	Yes		ASAP (PDUFA Date: 11-27-00)

NAME OF FIRM:Clindagel, LLC (Target Research Associates)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: New Proprietary Name Consult

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Attn:Patrick Guinn

The Division is requesting a formal consult regarding the NDA 50-782 Clindagel (clindamycin phosphate) 1% Topical Gel - new proprietary name submission. The applicant is proposing Clindagel as proprietary names for consideration. Enclosed is a copy of the supporting documentation for their proposal.

Please call Indira Kumar at 827-2072 for further details. Thanks.

cc: Original NDA 50-782
HFD-540/Div. Files/Kumar/Wilkin/Walker/Huene/DeCamp/Turujman

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one):
/S/ 4/13/00	☒ MAIL ☐ HAND
NATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

Erythema, dryness and peeling of the skin are common occurrences in the population in general and in acne patients. These signs can sometimes be associated with acne, with common underlying predisposition to dry skin, or with personal habits, such as excessive washing. It would be difficult to find a population of 666 subjects with acne, but with no erythema, dryness, peeling, or irritation. Excluding any subject with erythema, dryness peeling or irritation at baseline might in essence lead to studying a biased subset of the population. The Sponsor and the Investigators felt that the local irritation present at baseline would not make treatment contraindicated, and would not interfere with their ability to evaluate the responses to treatment or local reactions.

At both the end of Phase II meeting held January 19, 1999, and the pre-NDA meeting held November 15, 1999, the Agency agreed with the inclusion/exclusion criteria established in the protocol, as well as the method of evaluating irritation also outlined in the protocol. In the discussion during this meeting, the Agency required that patients diagnosed with more severe acne be enrolled in this study, to be able to better define the clinical effects of Clindagel. The Sponsor expected that some patients with more severe acne would present with signs of irritation, dryness, erythema, or peeling, and did not want to exclude them from the study.

The results of the study are as follows. Erythema was the most common sign of local irritation noted at baseline, it was reported in 55 % of the subjects. At base line erythema was absent or mild in 88 % (586/667) of the subjects. Of those subjects with erythema 78 % (288/370) were mild, 19 % (71/370) were moderate and 3 % (10/370) were severe. Most of this erythema noted at base line could be attributed to the erythema that can be associated with the presence of inflamed acne lesions. To enter the study subjects were required to have 25-100 inflammatory acne lesions. When many acne lesions are present in an area there can be an associated erythema of the surrounding normal skin.

Peeling and dryness were noted much less frequently than erythema. Peeling and dryness were either absent or mild at base line in 99 % (658/667) and 98 % (651/667) of the subjects, respectively. Of those subjects with peeling at base line 10 % (8/84) were moderate. Of those subjects noted to have dryness at base line 13 % (15/119) were moderate. There was a single case of severe dryness with severe peeling reported.

Irritation was reported by the subjects when they were asked if their skin was irritated. No irritation at base line was reported by 78 % of the subjects. Most, 93 % (618/667), of the subjects reported no or mild irritation at base line. Of those who reported irritation 67 % (99/148) were mild, 26 % (38/148) were moderate, and 7% (10/148) were severe. Since this was an open-ended question to the subjects it is possible that some of this "irritation" was related to the acne.

There was a decline in the observed frequency of moderate and severe local irritation scores from baseline to endpoint in most treatment groups (Figure 2- NDA volume 1.19, page 74). There was an increase, in all groups, of the percentage of subjects with absent erythema, peeling, dryness, and irritation from baseline to endpoint (Table14.2.17- NDA volume 1.19, pages 198-201). These observations would suggest that the local signs and symptoms noted at baseline were not

clinically significant, some of the local reactions may have been related to the acne, and that these subjects were appropriate for enrollment.

In summary the sponsor would suggest that the erythema noted at base line was attributable at least in part if not primarily to the inflammatory nature of acne. The reported occurrence of peeling, dryness and the subjective complaint of irritation noted at base line were most commonly absent or mild and representative of these signs and symptoms in an acne population prior to any intervention. Therefore, the investigators felt that the local irritation present would not make treatment contraindicated and would not interfere with their ability to access the response to treatment or local reactions. In addition, these subjects were enrolled because there was no exclusion criteria to exclude them.

Please let me know if you have any questions regarding the contents of this submission.

Sincerely,

Jill A. Powers, RAC
Manager, Regulatory Affairs

TARGET RESEARCH ASSOCIATES
CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

October 31, 2000

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
9201 Corporate Boulevard
North 214
Rockville, MD 20850

RE: NDA 50-782
Clindagel, LLC, Santa Rosa, CA
Clindagel™ (Clindamycin Phosphate ——— gel), 1%
Indication: Once a day treatment of acne vulgaris
Submission of stability data update

Dear Dr. Wilkin:

Reference is made to NDA 50-782 for Clindagel™ (Clindamycin phosphate ——— gel), 1% for the once a day treatment of acne vulgaris submitted on January 27, 2000, and the commitments made in the NDA to provide updated stability data.

Based on the commitment, the following stability data are submitted:

- Primary stability study 115-G, month 18 stability tables and interim report.
- Primary stability study 140-G, month 18 stability tables and interim report.
- Auxiliary stability study 087, final report.
- Auxiliary stability study 091, final report.

The results obtained to date from the stability studies substantiate the proposed expiry dating of ——— for the drug product in all three fill sizes, 7.5 g, 42 g, 77 g when stored at controlled room temperature between 15° - 25°C (59° - 77°F).

Please let me know if you have any questions about the enclosed information.

Sincerely,

Jill A. Powers, RAC
Manager, Regulatory Affairs

554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Clindagel, LLC	October 31, 2000
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
707-793-2600	707-793-0145
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
4189 Chaparral Court Santa Rosa, CA 95409	Target Research Associates 554 Central Avenue New Providence, NJ 07974 Telephone: 908-464-7500 Fax: 908-464-3529

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 50-782

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
1% Clindamycin Phosphate, USP	Clindagel

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Clindamycin 2-(dihydrogen phosphate)	

DOSAGE FORM: Topical gel	STRENGTHS: 1% clindamycin phosphate	ROUTE OF ADMINISTRATION: Topical

(PROPOSED) INDICATION(S) FOR USE: Once a day treatment for acne vulgaris

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Cleocin-T gel Holder of Approved Application Pharmacia & Upjohn

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Updated stability information

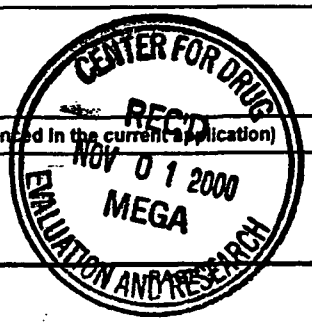
PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED ~~N/A~~ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attachment

All sites ready for inspection



Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

See attachment

FORM FDA 356h (4/00)

This application contains the following items: *(Check all that apply)*

- ☐ 1. Index
- ☐ 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
- ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
- ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
- ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(k)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER *(Specify)* Updated stability information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Robert J McCormack Ph.D.	Robert J. McCormack, Ph.D., VP, Regulatory Affairs Target Research Associates	October 31, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
554 Central Avenue New Providence, NJ 07974	(908)-464-7500

FDA/Target Research Associates/Fax Memo

Date: October 24, 2000

To: Jill Powers/Manager, Regulatory Affairs
(908) 464-7500 (P)
(908) 464- 3529 (F)

From: Indira Kumar, Regulatory Project Manager

Subject: NDA 50-782 Clinical Information Request – Absorption Spectrum and Severity of Local Irritation

Dear Ms. Powers,

1. It appears in the absorption spectrum submitted for Clindagel that the peak absorption is at ——nm, but this can not be precisely determined from the depiction provided. We would appreciate it if you would provide the wavelength of peak absorption.

2. For a determination of the incidence and severity of local irritation that occurred during the study, it would be helpful if an explanation could be provided for the presence of irritation, dryness, peeling, and erythema in many patients at baseline.

If you have questions, please call **Indira Kumar** at **(301) 827-2020.**

APPEARS THIS WAY
ON ORIGINAL