CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

64-159

Generic Name:	Clindamycin Phosphate Topical Solution USP, 1% (base)
Sponsor:	E. Fougera & Co.
Approval Date:	June 5, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-159

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	X
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-159

APPROVAL LETTER

AADA 64-159

JUN - 5 1997

E. Fougera & Co.
Division of Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

Dear Madam:

This is in reference to your abbreviated antibiotic application dated August 10, 1995, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Clindamycin Phosphate Topical Solution USP, 1% (base).

Reference is also made to your amendment dated May 8, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Clindamycin Phosphate Topical Solution USP, 1% (base) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Cleocin T® Topical Solution 1% (base) of Pharmacia and Upjohn).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-159

FINAL PRINTED LABELING

fougera®

CLINDAMYCIN PHOSPHATE TOPICAL SOLUTION USP, 1%

Use

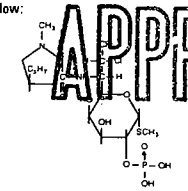
DESCRIPTION

Clindamycin Phosphate Topical Solution contains clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per milliliter.

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.

The solution contains isopropyl alcohol 50% v/v, propylene glycol, and water.

The structural formula is represented below:



Molecular Formula: $C_{18}H_{34}ClN_2O_5S$ Molecular Weight: 504.96

The chemical name for clindamycin phosphate is 7(S)-chloro-7-deoxylincomycin-2-phosphate.

CLINICAL PHARMACOLOGY

Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

Following multiple topical applications of clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per mL in an isopropyl alcohol and water solution, very low levels of clindamycin are present in the serum (0–3 ng/mL) and less than 0.2% of the dose is recovered in urine as clindamycin.

Clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of Clindamycin Phosphate Topical Solution for 4 weeks was 597 mcg/g of comedonal material (range 0–1490). Clindamycin *in vitro* inhibits all *Propionibacterium acnes* cultures tested (MICs 0.4 mcg/mL). Free fatty acids on the skin surface have been decreased from approximately 14% to 2% following application of clindamycin.

INDICATIONS AND USAGE

Clindamycin Phosphate Topical Solution is indicated 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

Clindamycin Phosphate Topical Solution 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 cultures 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. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg to 2 grams of vancomycin orally per day in three

to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

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: Clindamycin Phosphate Topical Solution contains an alcohol base which will cause burning and irritation of the eye. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucous membranes), bathe with copious amounts of cool tap water. The solution has an unpleasant taste and caution should be exercised when applying medication around the mouth.

Clindamycin Phosphate 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.

Pregnancy: Teratogenic Effects—*Pregnancy Category B*. Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin ranging from 100 to 600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to clindamycin. 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 Clindamycin Phosphate. 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 pediatric patients under the age of 12 has not been established.

ADVERSE REACTIONS

In 18 clinical studies of various formulations of Clindamycin Phosphate Topical solution using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events [see table below].

	Number of patients reporting events		
Treatment Emergent Adverse Event	Solution n = 553 (%)	Gel n = 148 (%)	Lotion n = 160 (%)
Burning	62 (11)	15 (10)	17 (11)
Itching	36 (7)	15 (10)	17 (11)
Burning/Itching	60 (11)	# (–)	# (–)
Dryness	105 (19)	34 (23)	29 (18)
Erythema	86 (16)	10 (7)	22 (14)
Oiliness/Oily Skin	8 (1)	26 (18)	12* (10)
Peeling	61 (11)	# (–)	11 (7)

not recorded
* of 126 subjects

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.

OVERDOSAGE

Topically applied clindamycin topical solution can be absorbed in sufficient amounts to product system effects (see **WARNINGS**).

DOSAGE AND ADMINISTRATION

Apply a thin film of Clindamycin Phosphate Topical Solution twice daily to affected area.

Keep container tightly closed.

HOW SUPPLIED

Clindamycin Phosphate Topical Solution containing clindamycin phosphate equivalent to 10 mg clindamycin per milliliter is available in the following sizes:

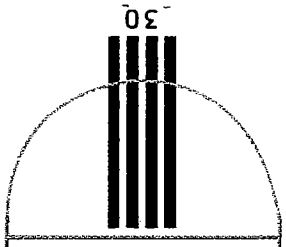
30 mL applicator bottle—NDC 0168-0201-30 60 mL applicator bottle—NDC 0168-0201-60

Store at controlled room temperature 15°–30°C (59°–86°F). Protect from freezing. Flash Point 75°F.

CAUTION: Federal law prohibits dispensing without prescription.

E. Fougera & Co.
a division of Altana Inc.
Melville, NY 11747

R3/96



NDC 0168-0201-60
fougera®
CLINDAMYCIN PHOSPHATE
Topical Solution USP, 1%

JUN 5 1997

NDC 0168-0201-60

fougera®

CLINDAMYCIN PHOSPHATE
Topical Solution USP, 1%

Equivalent to 1% (10 mg/mL) clindamycin

For External Use Only

Caution: Federal law prohibits dispensing without prescription.

60 mL

E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747

Store at controlled room temperature 15°-30°C (59°-86°F).
Flash Point 75°F.
Usual Dosage: See Package Insert for complete product information.
Avoid Contact With Eyes. Keep Container Tightly Closed.
Each mL contains: Clindamycin phosphate equivalent to clindamycin 1%. Also, propylene glycol; isopropyl alcohol, 50% (v/v); and purified water.
pH range 4.0-7.0.

NDC 0168-0201-60

fougera®

CLINDAMYCIN PHOSPHATE
Topical Solution USP, 1%

Equivalent to 1% (10 mg/mL) clindamycin

For External Use Only

Caution: Federal law prohibits dispensing without prescription.

60 mL

E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747

To use enclosed applicator:
1. Remove cap and discard.
2. Firmly press applicator into bottle.
3. Seal firmly by tightening domed-cap.

Patient Information:
1. Clean and dry the skin area to be treated.
2. Apply a thin film of medication to the affected area. Use sparingly, avoiding eyes and mouth. If medication accidentally enters eyes, rinse thoroughly with tap water.
3. Use dabbing motion of the tip rather than a rolling action. If tip becomes dry, invert bottle and depress tip several times until it becomes moist.

P4157
R5/96

APPROVED

N 3 0168-0201-60 3

Name: Clindamycin Sol 60 mL Carton
Die Size: 1.4375 x 1.4375 x 3.375
UPC Code: 0168-0201-30
Pharma Code: #60
Colors: PMS Yellow PMS Black

Name: Clindamycin Sol 30 mL Carton
Die Size: 1.25 x 1.25 x 3.875
UPC Code: 0168-0201-30
Pharma Code: #29
Colors: PMS Yellow PMS Black

EXP.

LOT

NDC 0168-0201-60

fougera®

CLINDAMYCIN PHOSPHATE

Topical Solution USP, 1%

Equivalent to 1%
(10 mg/mL) clindamycin

For External Use Only

Caution: Federal law prohibits dispensing without prescription.

60 mL

E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747

Avoid Contact with eyes.
Store at controlled room temperature 15°-30°C (59°-86°F). Flash Point 75°F.
Keep Container Tightly Closed.
Store in an upright fashion.
Each mL contains:
Clindamycin phosphate equivalent to clindamycin 1%. Also, propylene glycol; isopropyl alcohol, 50% (v/v); and purified water.
pH range 4.0-7.0.
Usual Dosage: See Package Insert for complete product information.
L220160 RS/96

Patient Information:
1. Clean and dry skin area to be treated.
2. Apply a thin film of medication to the affected area. Use sparingly avoiding eyes and mouth. If medication accidentally enters eyes, rinse thoroughly with tap water.
3. Use dabbing motion of the tip rather than rolling action. If tip becomes dry invert bottle and depress tip several times until it becomes moist.

APPROVED

JUN 5 1997

Name: Clindamycin Sol 60 mL label
Size: 3.5 x 2.5
NDC#: 0168-0201-360
Pharma Code: #30
Colors: PMS Yellow PMS Black

EXP. LOT

Patient Information:
1. Clean and dry skin area to be treated.
2. Apply a thin film of medication to the affected area. Use sparingly avoiding eyes and mouth. If medication accidentally enters eyes, rinse thoroughly with tap water.
3. Use dabbing motion of the tip rather than rolling action. If tip becomes dry invert bottle and depress tip several times until it becomes moist.

NDC 0168-0201-30

fougera®

CLINDAMYCIN PHOSPHATE

Topical Solution USP, 1%

Equivalent to 1% (10 mg/mL) clindamycin

For External Use Only

Caution: Federal law prohibits dispensing without prescription.

30 mL

E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747

Avoid Contact with eyes.
Store at controlled room temperature 15°-30°C (59°-86°F). Flash Point 75°F.
Keep Container Tightly Closed.
Store in an upright fashion.
Each mL contains: Clindamycin phosphate equivalent to clindamycin 1%. Also, propylene glycol; isopropyl alcohol, 50% (v/v); and purified water.
pH range 4.0-7.0.
Usual Dosage: See Package Insert for complete product information.
L220130 R5/96

JUN 5 1997

APPROVED

Name: Clindamycin Sol 30 mL label
Size: 2.875 x 1.875
NDC#: 0168-0201-30
Pharma Code: #29
Colors: PMS Yellow PMS Black

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-159

CSO LABELING REVIEW(S)

"APPROVAL SUMMARY"

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: 7/22/96 **Date of Submission: JULY 2, 1996**

Secondary Reviewer: Angela Payne

AADA Number: 64-159 **Review Cycle: #2**

Applicant's Name [as seen on 356(h)]: E. Fougera & Co.

Manufacturer's Name (If different than applicant): Same

Proprietary Name: None

Established Name: Clindamycin Phosphate Topical Solution USP, 1% (base)

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

[NOTE: These deficiencies can be located on the x-drive as detailed in notes from Ted Sherwood regarding the New X-Drive]

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30 mL and 60 mL submitted July 2, 1996

Carton Labeling: 30 mL and 60 mL submitted July 2, 1996

Professional Package Insert Labeling: Submitted July 2, 1996

Revisions needed post-approval: none

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Cleocin T

NDA Number: 50-537

NDA Drug Name: Clindamycin Phospate Topical Solution USP, 1%

NDA Firm: Upjohn

Date of Approval of NDA Insert and supplement #: Approved February 22, 1884.

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance?
No

Basis of Approval for the Container Labels: Cleocin T

Basis of Approval for the Carton Labeling: Cleocin T

Other Comments: none

REVIEW OF PROFESSIONAL LABELING CHECK LIST

See check list completed January 24, 1996

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?			
Is this product a USP item? If so, USP supplement in which verification was assured.			
Is this name different than that used in the Orange Book?			
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.			
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.			
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.			
Does the package proposed have any safety and/or regulatory concerns?			
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			

Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?			
Is the strength and/or concentration of the product unsupported by the insert labeling?			
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			
Are there any other safety concerns?			
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).			
Has applicant failed to clearly differentiate multiple product strengths?			
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)			
Error Prevention Analysis: *LABELING* (Continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?			
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			
Do any of the inactives differ in concentration for this route of administration?			
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?			
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			

Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?			
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?			
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.			
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

G Payne
Primary Reviewer

7/23/96
Date

John J. Vezza for/
Acting Team Leader
Labeling Review Branch

7/24/96
Date

cc: AADA 64-159
Division File
HFD-613/APayne\AVezza
njg\7\22\96\ x:\new...fougera\ltrs&rev\64159ap.l
Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

Date of Review: January 24, 1996

Date of Submission: August 10, 1995

Primary Reviewer: Angela M. Payne

AADA Number: 64-159 **Review Cycle: #1 (major)**

Applicant's Name [as seen on 356(h)]: E. Fougera & CO.

Manufacturer's Name (If different than applicant): same

Proprietary Name: none

Established Name: Clindamycin Phosphate Topical Solution USP, 1% base

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

[NOTE: These deficiencies can be located on the x-drive as detailed in notes from Ted Sherwood regarding the New X-Drive]

A. CHEMISTRY DEFICIENCIES

B. LABELING DEFICIENCIES

1. CONTAINER: 30 mL and 60 mL

   a. Relocate "for External Use Only" to the main panel.

   b. Include the pH range.

c. Revise "See package..."to read as follows:

Usual Dosage: See package...

2. CARTON

a. See comments under CONTAINER.

b. Correct the spelling of "thoroughly" on the side panel under Patient Information .

c. Delete "—" which appears after "NDC".

3. INSERT

a. DESCRIPTION

Include the molecular formula.

b. CLINICAL PHARMACOLOGY

i. Delete the second paragraph

ii. Replace "—" with "mL". Revise throughout the insert.

iii. Last paragraph, line 3 - ...Phosphate Topical Solution...

c. WARNINGS

Revise the entire section as follows:

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 cultures 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. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

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

d. PRECAUTIONS

i. Add the following text after the General subsection:

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.

ii. Revise the pregnancy subsection heading as follows:

Pregnancy: Teratogenic Effects: Pregnancy Category B

iii. Nursing Mothers -

1) First sentence - "use" rather than "

2) Delete the third sentence
Replace it with "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."

iv. Pediatric Use - ... effectiveness in pediatric patients under the...

e. ADVERSE REACTIONS

Revise the entire section as follows:

In 18 clinical studies of various formulations of Clindamycin Phosphate Topical solution using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events [see table below].

Number of patients reporting events

Treatment Emergent Adverse Event	Solution n=553(%)	Gel n=148(%)	Lotion n=160(%)
Burning	62(11)	15(10)	17(11)
Itching	36 (7)	15(10)	17(11)
Burning/Itching	60(11)	#(-)	#(-)

Dryness	105(19)	34(23)	29(18)
Erythema	86(16)	10(7)	22(14)
Oiliness/Oily Skin	8(1)	26(18)	12*(10)
Peeling	61(11)	#(-)	11 (7)

not recorded
* of 126 subjects

Orally and parenterally administered clinidamyci 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 formulation 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.

f. Add the OVERDOSAGE section

OVERDOSAGE

Topically applied clindamycin topical solution can be absorbed in sufficient amounts to produce system effects (See WARNINGS)

g. HOW SUPPLIED

Add "protect from freezing."

Please revise your labels and labeling, as instructed above, and submit final printed containers labels and carton labeling and draft insert labeling (final print if you prefer).

FOR THE CHEMIST:

Please verify the amount of alcohol calculated for use.

FOR THE RECORD:

1. Review based on the listed drug (Cleocin T; NDA 50537; Upjohn; Approved February 22, 1994)

2. There are no patents or exclusivity issues with this product.

3. Package sizes are 30 mL and 60 mL for the innovator and generic.

4. Inactive ingredients are consistent with composition statement on page 52 vol 1.1

5. Storage/Dispensing information:

   USP: Keep in tight containers
   AADA: CRT; keep container tightly closed: store in an upright fashion.
   NDA: Same.

Established Name: Clindamycin Phosphate Topical Solution

Is this the same name, as seen on the Acceptance to File, letter? YES

Is this product a USP item? Yes

List the USP supplement in which verification was assured:

What is the name used in the Orange Book? Clindamycin phosphate; solution; topical

Has the product name been proposed in the PF?

ERROR PREVENTION ANALYSIS

A. PROPRIETARY NAME :none

B. PACKAGING: See FTR

d. Are individual cartons required? Yes No
Factors to consider are:
1) Does the innovator have individual cartons?
Yes
2) Is the product sensitive to light and is it unlikely that the product will be retained inside a multiple unit carton until the time of use or until the contents have been used?
Yes No
3) Is there a need for the package insert to accompany the product?
Yes

e. Any other concerns?

C. LABELING:

1. Is the name of the drug clearly printed and is it the most prominent information on the label? YES

2. Is the strength clearly expressed? yes

3. Are multiple strengths of the same product clearly differentiated? n/a

4. Is the corporate logo larger than one-third the size of the container label? NO [NOTE: not a requirement, but seen in the ASHP Guidelines].

5. Does the color of the label relay any special

significance to the professional (i.e. Synthroid and Premarin have a matching container color with the color of the tablet)? No

6. Does the RLD make special differentiation for this label (i.e., Pediatric strengths vs Adult or Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA, would be required for the ANDA)? Yes No

7. Is the Manufactured By/Distributor statement correct and consistent between labels and labeling? YES

8. If a unit-dose carton, does it contain the child-resistant statement? n/a

9. Is the most recently approved innovator labeling being used as a model? To determine this, use the MIS to determine the most recent labeling supplement approval date for the NDA. This MIS data is to be printed and attached to the first review and the final review as confirmation that the correct model is being used.

10. For solid oral dosage forms, have identifying markings (imprints, embossing, debossing) been described in the HOW SUPPLIED section?

11. Has the firm adequately supported any compatibility or stability claims which appear in the insert labeling? Include information describing where the chemist has confirmed the data has been adequately supported.

SCORING: n/a

INACTIVE INGREDIENTS:

On what page of the application are the inactive ingredients listed: page 52 vol 1.1

Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? YES

Have all of the inactives previously been used in this concentration for this route of administration?

Any adverse effects anticipated from the inactive NO. ingredients (i.e. benzyl alcohol in neonates)?

Are all the inactives cited in the composition statement listed in the DESCRIPTION section? Yes

---

USP ISSUES:

List the USP/NDA/ and ANDA dispensing recommendations: SEE for the record above.

Do the container recommendations meet or exceed these recommendations? yes

Does the USP have any labeling recommendations? No

If any, does the ANDA meet the requirements?

Is the product light sensitive? No

If yes, is the NDA in a light-resistant container?

If yes, is the ANDA in a light-resistant container?

Does the USP Description and Solubility information agree with the information appearing in the insert labeling? If not, the USP information should be used. However, since the USP often lists numerous solvents, please include only those which appear in the innovator labeling.

Storage recommendations of the USP/NDA/ANDA: SEE FTR

If the storage recommendations differ from the USP or the innovator, have they been adequately supported and is the difference acceptable?

BIOEQUIVALENCY ISSUES: Bio pending (possible waiver for solutions)

Does the insert labeling have any reference to a food effect or a no-effect? NO.

Has the CLINICAL PHARMACOLOGY section of the insert labeling, as seen in the NDA, been modified for this ANDA? NO

If yes, briefly indicate where and why:

List the bioequivalency values, for appropriate dosage forms, found in the insert labeling and list the values as seen in the approved bio study (i.e., Cmax, Tmax, T1/2, AUC):

Date Bioequivalency Study found Acceptable:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

What is the RLD on the 356(h) form:

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance?
Yes No

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels:

Basis of Approval for the Carton Labeling:

Other Comments:

PATENT/EXCLUSIVITY ISSUES: SEE FTR

List the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity:

Expiration date and listing of all patents, exclusivities etc.:

NOTES/QUESTIONS TO THE CHEMIST: See ABOVE

FOR THE RECORD: SEE above.

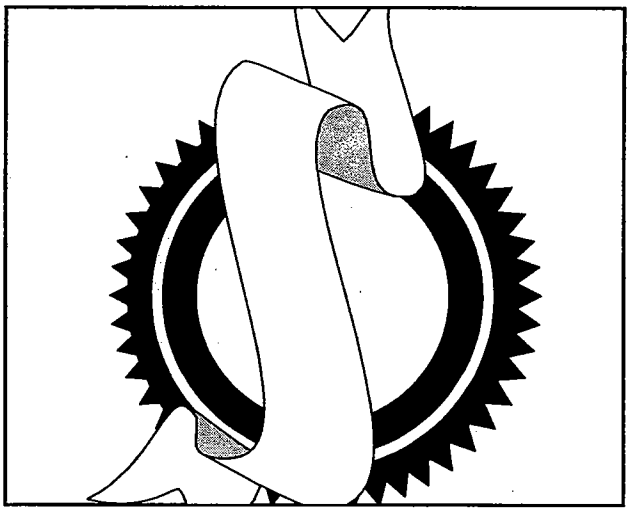
Primary Reviewer — Date 2/26/96

Chief, Labeling Rev. Branch — Date 2-26-96

cc:

AADA 64-159
HFD-613/APyane\CHoppes
njg/2/26/96/x:\new...fougera\lets&rev\64159na1.ld
Review

Phillips 2/27/96



APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-159

CHEMISTRY REVIEW(S)

AADA APPROVAL SUMMARY

AADA: 64-159

FIRM: E. Fougera & Co., Division of Altana Inc.

DRUG PRODUCT: Clindamycin Phosphate Topical solution USP, 1% (base)

DOSAGE FORM: Topical Solution **STRENGTH:** 1%

CAMP STATEMENT/EIR UPDATE STATUS: Acceptable EER dated 12/5/96

BIO STUDY: The waiver of in-vivo bioequivalence study was granted 3/28/96.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Sample validation: acceptable (see report dated 10/30/96).

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION): The containers used in the stability studies were identical to those described in the container section.

LABELING: FPL found satisfactory by A.Payne 7/22/96.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): N/A

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

Stability Lot #6448 was filled into 30 mL (total ——— and 60 mL ——— bottles. The intended maximum batch size is ———. According to our OGD guidelines, the allowed maximum batch would be ——— in 30 mL bottle size and ——— in 60 mL bottle size based on their exhibit sample validation data.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): See above

Specifications for active ingredient: Under #23A
Specifications for the finished product: For Release see under #28; for Stability see under #29

CHEMIST: Maria C. Shih **DATE:** 12/4/96 12/9/96

SUPERVISOR: John Harrison **DATE:** 12/4/96

1. CHEMIST'S REVIEW NO. #1

2. AADA #64-159

3. NAME AND ADDRESS OF APPLICANT

E. Fougera & Co.
Division of Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

Telephone: 516-454-7677

4. LEGAL BASIS FOR SUBMISSION
21 CFR §453.522a

Reference drug: Cleocin T® (Clindamycin Phosphate) 1% Topical Solution manufactured by Upjohn. Signed certifications are provided (pp. 04-5) stating that there are no unexpired patents and that the drug is not subject to any exclusivity determination.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

Clindamycin Phosphate Topical Solution USP, 1% (base)

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
Original Submission: 8/10/95
(Amendment 10/2/95)

FDA:
Acknowledgment: 10/18/95
("Refuse to File" letter 9/26/95)

10. PHARMACOLOGICAL CATEGORY

Antibacterial

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

See DMF list under #37

13. DOSAGE FORM

Solution (Topical)

14. POTENCY

1% (as clindamycin)

15. CHEMICAL NAME AND STRUCTURE

$C_{18}H_{34}ClN_2O_8PS$ M.Wt.= 504.97

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)

16. RECORDS AND REPORTS
N/A

17. COMMENTS

This application is nicely prepared. Except concerns regarding specifications and stability studies, information and data submitted for chemistry issues are generally satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approvable (MAJOR)

19. REVIEWER: DATE COMPLETED:

Maria C. Shih 2/26/96

Redacted 9

Page(s) of trade secret and /or confidential commercial information

1. CHEMIST'S REVIEW NO. #2

2. AADA #64-159

3. NAME AND ADDRESS OF APPLICANT

E. Fougera & Co.
Division of Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

Telephone: 516-454-7677

4. LEGAL BASIS FOR SUBMISSION
21 CFR §453.522a

Reference drug: Cleocin T® (Clindamycin Phosphate) 1% Topical Solution manufactured by Upjohn. Signed certifications are provided (pp. 04-5) stating that there are no unexpired patents and that the drug is not subject to any exclusivity determination.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

Clindamycin Phosphate Topical Solution USP, 1% (base)

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
Original Submission: 8/10/95
(Amendment 10/2/95)

FDA:
Acknowledgment: 10/18/95
("Refuse to File" letter 9/26/95)

For this review:
Amendment 7/2/96 to N/A letter 3/15/96

10. PHARMACOLOGICAL CATEGORY

Antibacterial

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

See DMF list under #37

13. DOSAGE FORM

Solution (Topical)

14. POTENCY

1% (as clindamycin)

15. CHEMICAL NAME AND STRUCTURE

$C_{18}H_{34}ClN_2O_8PS$ M.Wt.= 504.97

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)

16. RECORDS AND REPORTS
N/A

17. COMMENTS
In Amendment 7/2/96 Firm responds to our concerns in order:

Q1. Your specification for the active ingredient under "Related substances" is misleading due to the omission of solution (1) and solution (2) (Ref. BP 1993, Volume 1, page 165). Please revise.

A1. The specifications for the active ingredient have been revised to clarify the Related Substances test specification (Attachment 1).

Comments:
Firm includes specifications for both [redacted] In the original submission only [redacted] was identified as the [redacted] Ask Firm to clarify.

Q2. Please identify some of the individual impurities.

A2. Firm lists potential individual impurities and their HPLC relative retention times (RRT) with respect to clindamycin phosphate:

RRT	Compound
[redacted]	[redacted]

Redacted 10

Page(s) of trade secret and /or confidential commercial information

1. CHEMIST'S REVIEW NO. #3

2. AADA #64-159

3. NAME AND ADDRESS OF APPLICANT

E. Fougera & Co.
Division of Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

Telephone: 516-454-7677

4. LEGAL BASIS FOR SUBMISSION
21 CFR §453.522a

Reference drug: Cleocin T® (Clindamycin Phosphate) 1% Topical Solution manufactured by Upjohn. Signed certifications are provided (pp. 04-5) stating that there are no unexpired patents and that the drug is not subject to any exclusivity determination.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Clindamycin Phosphate Topical Solution USP, 1% (base)

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
Original Submission: 8/10/95
(Amendment 10/2/95)

FDA:
Acknowledgment: 10/18/95
("Refuse to File" letter 9/26/95)

Amendment 7/2/96 to N/A letter 3/15/96

Amendment 10/30/96 to N/A letter 8/15/96

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

See DMF list under #37

13. DOSAGE FORM

Solution (Topical)

14. POTENCY

1% (as clindamycin)

15. CHEMICAL NAME AND STRUCTURE

$C_{18}H_{34}ClN_2O_8PS$ M.Wt.= 504.97

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)

16. RECORDS AND REPORTS
N/A

17. COMMENTS

In Amendment 10/30/96 Firm responds in order:

Q1. We note that you include the revised specifications for both [redacted] In the original submission only [redacted] was identified as the [redacted] Please clarify.

A1. Firm states that it was a mistake to include the [redacted] specifications. They may supplement the application for [redacted] source post approval; presently [redacted] is the only [redacted] for the [redacted]

Q2. [redacted]

A2. [redacted]

Q3. Please explain in detail the assay procedures for Clindamycin Phosphate potency and for the degradant content of the final product as reported in the stability studies.

A3. The assay procedure for potency and degradation product levels used at the initial time point was essentially the USP HPLC procedure. [redacted] was added to the standard solution so that [redacted], the major degradation products of clindamycin phosphate, could be assayed simultaneously. Any other degradation products were assayed against the [redacted]

The assay method was revised between the one month and two month stability intervals as detailed in text (no longer using an internal standard).

The validation data of the assay procedures are attached. The specifications (in process, release, and stability) provided in Attachments 5, 6, and 7 are the same as those provided in Amendment 7/2/96.

Labeling: satisfactory per A.Payne 7/24/96.

Bio waiver: granted 3/28/96.

Sample validation: satisfactory 10/30/96.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval recommended (pending EER) Unacceptable EER signed 12/5/96

19. REVIEWER: DATE COMPLETED:

Maria C. Shih 12/4/96

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ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-159

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 64-159 **SPONSOR:** FOUGERA

DRUG & DOSAGE FORM: CLINDAMYCIN PHOSPHATE, U.S.P.; TOPICAL SOLUTION.

STRENGTH/(s): 1%

TYPE OF STUDY: Single/Multiple (N/A) Fasting/Food (N/A)

STUDY SITE: (N/A)

STUDY SUMMARY:

Waiver Granted based on fulfilling CFR 320.22(b)(3).

Formulation Q&Q; Review attached.

DISSOLUTION: (N/A)

PRIMARY REVIEWER: A.P. PATEL **BRANCH:** 3

INITIAL: AP **DATE:** 12/16/96

BRANCH CHIEF: Dr. R.M. Mhatre **BRANCH:** 3

INITIAL: RMM **DATE:** 12/17/96

ACTING DIRECTOR DR. R. PATNAIK.
DIVISION OF BIOEQUIVALENCE

INITIAL: [signature] **DATE:** 1/7/97

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: _____ **DATE:** _____

MAR 26 1996

Clindamycin Phosphate, USP
1% Topical Solution
AADA # 64-159
Reviewer: A.P.Patel
wp# x:\apatel\64159w.895

Fougera
Melville, N.Y.
Submission Date:
Aug. 10, 1995
Oct. 2, 1995

Review of a Waiver Request

Background:

Original submission Aug. 10, 1995, Agency refused to file (Sep. 26, 1995). The firm failed to demonstrate qualitative and **quantitatively** the proposed product was same as the reference listed drug product. The firm resubmitted the application on Oct. 2, 1995.

Introduction:

Clindamycin phosphate is used in the treatment of acne vulgaris.

Objective:

The firm is requesting a waiver of the *in-vivo* bioequivalence requirements for their clindamycin phosphate 1% topical solution, USP. The waiver request is based upon comparable formulation to the reference product Cleocin T manufactured by Upjohn.

Comments:

1. The product meets the criteria for waiver of the *in-vivo* bioequivalence study requirements set forth in CFR 320.22(b)(3).

a. The test product is a topical solution.

b. It contains an active drug moiety in the same concentration as a drug product that is the subject of an approved full NDA.

Deficiencies: None

Recommendation:

1.The Division of Bioequivalence agrees that the information submitted by Fougera demonstrates that its clindamycin phosphate 1% topical solution falls under 21 CFR 320.22 b(3)(i). Therefore, the waiver of *in vivo* bioequivalence study requirements for clindamycin phosphate 1% topical solution is granted. The test product, clindamycin phosphate 1% topical solution is deemed bioequivalent to Cleocin T, 1% topical solution manufactured by Upjohn.

The firm should be advised of the recommendation.

3/25/96

A.P.Patel
Division of Bioequivalence
Review Branch III

RD Initialed R.M. Mhatre
FT Initialed R.M. Mhatre Ramakant M. Mhatre Date: 3/26/96

Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

ANDA# 64-159 (Original, Duplicate), HFD-600 (Hare), HFD-630, HFD-658 (R.M.Mhatre, A.P.Patel), Drug File, Division File.

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Comparative formulations:
For the test and reference clindamycin phosphate 1% topical solutions.

Table 1

	Reference	Test
Ingredients	***Cleocin T**	**Fougera**
Clindamycin Phosphate	10 mg/ ml	10 mg/ ml
Isopropyl Alcohol	50% v/v	50% v/v
Propylene Glycol	[redacted]	[redacted]
[redacted]		
[redacted]		
[redacted], Water, USP		

* The firm had the reference product analyzed by Atlanta, Inc.

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Formulation

Redacted 1

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-159

ADMINISTRATIVE DOCUMENTS

E L E C T R O N I C M A I L M E S S A G E

Date: 03-Jan-1997 03:59pm EST
From: Maria Shih
SHIH
Dept: HFD-643 MPN2 279
Tel No: 301-594-0360 FAX 301-594-3839

TO: Jason Gross (GROSSJ)

CC: John Harrison (HARRISONJ)
CC: Mark Anderson (ANDERSONM)

Subject: RE: clindamycin

We are trying to have the approval of AADA 64-159 (Clindamycin Topical Solution) because the EER problem with [redacted]can be resolved (there is a misunderstanding; I have a memo here if you want to read it). Please check with Bob West and Mr. Harrison for the current development.

AADA 64-187 is for Erythromycin Topical Solution. Altana [redacted] like their other application 64-184. It is confusing sometimes.

Thanks for your attention.

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 06-Jan-1997 07:25am EST
From: Robert West
WESTR
Dept: HFD-617 MPN2 113
Tel No: 301-594-0375 FAX 301-594-0180

TO: Edwin Rivera (RIVERA)

CC: 6 addressees

Subject: AADA 64-159 - Clindamycin Phosphate - [redacted]

Edwin:

We currently have AADA 64-159 submitted by Fougera for Clindamycin Phosphate Topical Solution, USP. The [redacted] is [redacted] We are also aware of a recent letter you sent to [redacted] concerning CGMP deficiencies as a result of a recent inspection. However, we note that the letter states that your office will recommend disapproval of all applications listing [redacted].

Since your letter did not specifically mention [redacted], are you able to recommend approval for [redacted]

This application by Fougera is otherwise ready for approval in OGD.

Please advise.

Thanks,

Bob

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 08-Jan-1997 08:04am EST
From: Jason Gross
GROSSJ
Dept: HFD-615 MPN2 113
Tel No: 301-594-2290 FAX 301-594-0181

TO: Robert West (WESTR)

CC: 6 addressees

Subject: RE: AADA 64-159 - Clindamycin Phosphate -

Bob...

On 12/3/96, we also added a new facility "applied analytical" and we are awaiting the EER for that facility. — AC

Depending on the reply from compliance we will either issue a NA-letter or hold the application pending the outcome for applied analytical.

FYI
JAG

APPEARS THIS WAY
ON ORIGINAL

E L E C T R O N I C M A I L M E S S A G E

Date: 30-Jan-1997 03:53pm EST
From: Edwin Rivera
RIVERA
Dept: HFD-322 MPN1 272
Tel No: 301-594-0095 FAX 301-594-2202

TO: Robert West (WESTR)

CC: 9 addressees

Subject: RE: AADA 64-159 - Clindamycin Phosphate -

Robert:

Upon receipt of your E-Mail of January 6, 1997 regarding the approval status of I reviewed our inspection files and determined that our last inspections covering this API were in October 19 - 20, 1992 and May 12 - 13, 1988. Both inspections disclosed only minor CGMP deficiencies and were classified as VAI and NAI, respectively.

I then contacted and learned that Clindamycin Phosphate is As you already know, the April 1996 inspection revealed that the firm was in the process of qualifying its production area, was revising master production records and operating procedures to bring this facility into CGMP compliance.

I requested a status report from on the pending issues resulting from the April 1996 inspection. The firm has informed me that the and that validation of both systems should be completed by April 1997. The revision of master production records and operating procedures have also been completed and these documents will be made available to FIT for our review by January 31, 1997. has also reported that their revalidation campaign for batches of will be completed by April 1997, with revalidation of to follow later in the year.

The firm has contacted DEIO to arrange for reinspection of the facility in April or May 1997. We will contact DEIO and request that they also cover the manufacture of Clindamycin Phosphate during the reinspection. Unless you have a pressing need to approve AADA 64-159, I recommend that we wait until the reinspection shows that the firm is in CGMP compliance for the produced by

Edwin Rivera

E L E C T R O N I C M A I L M E S S A G E

Date: 09-May-1997 10:48am EDT
From: Jason Gross
GROSSJ
Dept: HFD-324 MPN1 265
Tel No: 301-827-0062 FAX 301-827-0145

TO: Mark Anderson (ANDERSONM)

CC: Melissa Egas (EGASM)

Subject: N 64159/000 FOugera, Clindamycin

Mark..

Heads up I just got a call from Virginai Carmen of fougeria advising me that the firm " ——— was inspected.

EES does not show we have received the results of the inspection yet... but I am sure they will be forthcoming.

Good luck
JAG

APPEARS THIS WAY ON ORIGINAL

ration, and record the peak responses as directed under *Procedure:* the relative standard deviation for replicate injections is not more than 2.5%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{18}H_{33}ClN_2O_5S$ in each mL of the Injection taken by the formula:

$$(10/7)(CP/V)(R_U/R_S),$$

in which C is the concentration, in mg per mL, of USP Clindamycin Phosphate RS in the *Standard preparation*, P is the potency, in µg of $C_{18}H_{33}ClN_2O_5S$ per mg of the USP Clindamycin Phosphate RS, V is the volume, in mL, of Injection taken, and R_U and R_S are the ratios of the response of the clindamycin phosphate peak to the response of the internal standard peak obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Clindamycin Phosphate Topical Solution

» Clindamycin Phosphate Topical Solution contains the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of clindamycin ($C_{18}H_{33}ClN_2O_5S$).

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Clindamycin Phosphate Reference Standard*—Do not dry before using.

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation*, both relative to the internal standard, as obtained in the *Assay*.

pH ⟨791⟩: between 4.0 and 7.0.

Assay—

Mobile phase, *Internal standard solution*, *Standard preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Clindamycin Phosphate*.

Assay preparation—Transfer an accurately measured volume of Clindamycin Phosphate Topical Solution, equivalent to about 20 mg of clindamycin, to a 100-mL volumetric flask, add 25.0 mL of *Internal standard solution*, dilute with *Mobile phase* to volume, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Clindamycin Phosphate*. Calculate the quantity, in mg, of $C_{18}H_{33}ClN_2O_5S$ in each mL of the Topical Solution taken by the formula:

$$0.1(CP/V)(R_U/R_S),$$

in which V is the volume, in mL, of Topical Solution taken, and the other terms are as defined therein.

Sterile Clindamycin Phosphate

» Sterile Clindamycin Phosphate is Clindamycin Phosphate suitable for parenteral use. It has a potency equivalent to not less than 758 µg of clindamycin ($C_{18}H_{33}ClN_2O_5S$) per mg, calculated on the anhydrous basis.

Packaging and storage—Preserve in *Containers for Sterile Solids* as described under *Injections* ⟨1⟩.

Reference standard—*USP Clindamycin Phosphate Reference Standard*—Do not dry before using.

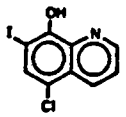
Depressor substances—It meets the requirements of the *Depressor Substances Test* ⟨101⟩, the test dose being 1.0 mL per kg of a solution prepared to contain 5.0 mg of clindamycin ($C_{18}H_{33}ClN_2O_5S$) per mL in sterile saline TS.

Pyrogen—It meets the requirements of the *Pyrogen Test* ⟨151⟩, the test dose being 1.0 mL per kg of a solution prepared to contain 24 mg of clindamycin ($C_{18}H_{33}ClN_2O_5S$) per mL in pyrogen-free saline TS.

Sterility—It meets the requirements under *Sterility Tests* ⟨71⟩, when tested as directed in the section, *Test Procedure Using Membrane Filtration*, 6 g of specimen aseptically dissolved in 200 mL of *Fluid A* being used.

Other requirements—It conforms to the definition, responds to the *Identification test*, and meets the requirements for *pH*, *Water*, *Crystallinity*, and *Assay* under *Clindamycin Phosphate*.

Clioquinol



C_9H_5ClINO 305.50
8-Quinolinol, 5-chloro-7-iodo-.
5-Chloro-7-iodo-8-quinolinol [*130-26-7*].

» Clioquinol, dried over phosphorus pentoxide for 5 hours, contains not less than 93.0 percent and not more than 100.5 percent of C_9H_5ClINO (the 5-chloro-7-iodo-8-quinolinol isomer).

Packaging and storage—Preserve in tight, light-resistant containers.

Reference standard—*USP Clioquinol Reference Standard*—Dry over phosphorus pentoxide for 5 hours before using.

Identification—

A: Prepare a Standard solution as directed for *Standard preparation* in the *Assay*, except to use 1.0 mL of pyridine instead of the *Internal standard solution*, and chromatograph as directed in the *Assay:* the chromatogram of the *Assay preparation* obtained in the *Assay* exhibits a peak for clioquinol, the retention time of which corresponds with that exhibited by the Standard solution.

B: The ultraviolet absorption spectrum of a 1 in 200,000 solution in 3 *N* hydrochloric acid exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Clioquinol RS, concomitantly measured, and the respective absorptivities, calculated on the dried basis, at the wavelength of maximum absorbance at about 267 nm do not differ by more than 3.0%.

C: Heat 100 mg with 5 mL of sulfuric acid: copious violet vapors of iodine are evolved.

Loss on drying ⟨731⟩—Dry it over phosphorus pentoxide for 5 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.5%.

Free iodine and iodide—Shake 1.0 g with 20 mL of water for 30 seconds, allow to stand for 5 minutes, and filter. To 10 mL of the filtrate add 1 mL of 2 *N* sulfuric acid, then add 2 mL of chloroform, and shake: no violet color appears in the chloroform (*free iodine*). To the mixture add 5 mL of 2 *N* sulfuric acid and 1 mL of potassium dichromate TS, and shake for 15 seconds: the color in the chloroform layer is no deeper than that produced in a control test made in the following manner: Dilute 2.0 mL of potassium iodide solution (1 in 6000) with water to 10 mL, add 6 mL of 2 *N* sulfuric acid, 1 mL of potassium dichromate TS, and 2 mL of chloroform, and shake for 15 seconds (*0.05% of iodide*).

Assay—

Internal standard solution—Prepare a solution of pyrene in pyridine containing 2 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Clioquinol RS in a mixture of pyridine and *n*-hexane (4:1) to obtain a Standard solution having a known concentration

$$(F/1000)(W_S/V)(R_U/R_S),$$

in which V is the volume, in mL, of constituted solution from Clindamycin Palmitate Hydrochloride for Oral Solution taken and the other terms are as defined therein.

Clindamycin Phosphate

$C_{18}H_{34}ClN_2O_8PS$ 504.96

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

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) [*24729-96-2*].

» Clindamycin Phosphate has a potency equivalent to not less than 758 μg of clindamycin ($C_{18}H_{33}ClN_2O_5S$) per mg, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Clindamycin Phosphate Reference Standard*—Do not dry before using.

Identification—The infrared absorption spectrum of a mineral oil dispersion of it, previously dried at 100° for 2 hours, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Clindamycin Phosphate RS, previously dried at 100° for 2 hours.

Crystallinity ⟨695⟩: meets the requirements.

pH ⟨791⟩: between 3.5 and 4.5, in a solution containing 10 mg per mL.

Water, *Method I* ⟨921⟩: not more than 6.0%.

Other requirements—Clindamycin Phosphate intended for use in making Clindamycin Phosphate Injection complies with the requirements for *Depressor substances* and *Pyrogen* under *Sterile Clindamycin Phosphate*.

Assay—

Mobile phase—Dissolve 10.54 g of monobasic potassium phosphate in 775 mL of water, and adjust with phosphoric acid to a pH of 2.5. Add 225 mL of acetonitrile, mix, and filter. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—Ensure that the concentration of acetonitrile in the *Mobile phase* is not less than 22% and not more than 25%, in order to retain the correct elution order.]

Internal standard solution—Prepare a solution of 4′-hydroxyacetophenone in acetonitrile containing about 4 mg per mL. Dilute a volume of this solution with *Mobile phase* to obtain a solution having a concentration of about 0.04 mg per mL.

Standard preparation—Transfer about 24 mg of USP Clindamycin Phosphate RS, accurately weighed, to a 100-mL volumetric flask. Add 25.0 mL of *Internal standard solution*, dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer about 24 mg of Clindamycin Phosphate, accurately weighed, to a 100-mL volumetric flask, add 25.0 mL of *Internal standard solution*, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure*: the resolution, R, between the analyte and internal standard peaks is not less than 2.0, and the relative standard deviation for replicate injections is not more than 2.5%.

Procedure—Separately inject equal volumes (about 20 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 1.0 for clindamycin phosphate and 1.2 for 4′-hydroxyacetophenone. Calculate the quantity, in μg, of $C_{18}H_{33}ClN_2O_5S$ in the portion of Clindamycin Phosphate taken by the formula:

$$100CP(R_U/R_S),$$

in which C is the concentration, in mg per mL, of USP Clindamycin Phosphate RS in the *Standard preparation*, P is the potency, in μg of $C_{18}H_{33}ClN_2O_5S$ per mg of the USP Clindamycin Phosphate RS, and R_U and R_S are the ratios of the response of the clindamycin phosphate peak to the response of the internal standard peak obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Clindamycin Phosphate Injection

» Clindamycin Phosphate Injection is a sterile solution of Sterile Clindamycin Phosphate or Clindamycin Phosphate in Water for Injection with one or more suitable preservatives and sequestering agents. It contains the equivalent of not less than 90.0 percent and not more than 120.0 percent of the labeled amount of clindamycin ($C_{18}H_{33}ClN_2O_5S$).

Packaging and storage—Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.

Reference standard—*USP Clindamycin Phosphate Reference Standard*—Do not dry before using.

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation*, both relative to the internal standard, as obtained in the *Assay*.

Pyrogen—When diluted with sterile pyrogen-free saline TS to a concentration of 24 mg of clindamycin ($C_{18}H_{33}ClN_2O_5S$) per mL, it meets the requirements of the *Pyrogen Test* ⟨151⟩, the test dose being 1.0 mL per kg.

pH ⟨791⟩: between 5.5 and 7.0.

Particulate matter ⟨788⟩: meets the requirements under *Small-volume Injections*.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Mobile phase—Dissolve 10.54 g of monobasic potassium phosphate in 775 mL of water, and adjust with phosphoric acid to a pH of 2.5. Add 225 mL of acetonitrile, mix, and filter. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—Ensure that the concentration of acetonitrile in the *Mobile phase* is not less than 22% and not more than 25% in order to retain the correct elution order.]

Internal standard solution—Prepare a solution of methylparaben in acetonitrile containing about 6 mg per mL. Dilute a volume of this solution with *Mobile phase* to obtain a solution having a concentration of about 0.06 mg per mL.

Standard preparation—Transfer about 24 mg of USP Clindamycin Phosphate RS, accurately weighed, to a 100-mL volumetric flask, add 25.0 mL of *Internal standard solution*, dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer an accurately measured volume of Clindamycin Phosphate Injection, equivalent to about 300 mg of clindamycin, to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 7.0 mL of the resulting solution to a 100-mL volumetric flask, add 25.0 mL of *Internal standard solution*, dilute with *Mobile phase* to volume, and mix.

Resolution solution—Prepare a solution of 4′-hydroxyacetophenone in acetonitrile containing about 4 mg per mL. Dilute a portion of the resulting solution with *Mobile phase* to obtain a solution having a concentration of about 0.04 mg per mL. Add about 25 mL of this solution to a 100-mL volumetric flask containing about 25 mg of USP Clindamycin Phosphate RS, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed under *Procedure*: the resolution, R, between clindamycin phosphate and 4′-hydroxyacetophenone is not less than 2.0. The relative retention times are 1.0 for clindamycin phosphate and about 1.2 for 4′-hydroxyacetophenone. Chromatograph the *Standard prepa-*

...CIN PHOSPHATE

...maintain serum ...lindamycin levels	Rapid infusion rate	Maintenance infusion rate
...above 4 mcg/mL	10 mg/min for 30 min	0.75 mg/min
...mcg/mL	15 mg/min for 30 min	1.00 mg/min
...g/mL	20 mg/min for 30 min	1.25 mg/min

...ADMINISTRATION

...rrhea occurs during therapy, this antibiotic should be discontinued. (See Warning box).

...eral (IM or IV Administration):

...ous infections due to aerobic gram-positive cocci and the susceptible anaerobes (NOT generally including *Bacteroides fragilis, Peptococcus* species and *Clostridium* species other than *Clostridium perfringens*):

...-1200 mg/day in 2, 3 or 4 equal doses.

...severe infections, particularly those due to proven or ...ted *Bacteroides fragilis Peptococcus* species, or *Clostridium* species other than *Clostridium perfringens*:

...-2700 mg/day in 2, 3 or 4 equal doses

...severe serious infections, these doses may have to be increased. In life threatening situations due to aerobes or anaerobes these doses may be increased. Doses of as much as ... daily have been given intravenously to adults. See ...ion and Infusion Rates section below.

...intramuscular injections of greater than 600 mg are not recommended.

...atively, drug may be administered in the form of a ...rapid infusion of the first dose followed by continuous ...sion as follows: [See table above.]

...ates (less than 1 month):

...5 mg/kg/day in 3 to 4 equal doses. The lower dosage ...is adequate for small prematures.

...ren (over 1 month of age): Parenteral (IM or IV) administration: 20 to 40 mg/kg/day in 3 or 4 equal doses. The ...r doses would be used for more severe infections. As an ...rnative to dosing on a body weight basis, children may be ...n on the basis of square meters body surface: 350 mg/m² ...day for serious infections and 450 mg/m²/day for more ...re infections.

...ntal therapy may be changed to oral CLEOCIN ...ATRIC© Flavored Granules (clindamycin palmitate ...drochloride) or CLEOCIN HCl© Capsules (clindamycin ...drochloride) when the condition warrants and at the discretion of the physician.

...-hemolytic streptococcal infections, treatment ...ued for at least 10 days.

...Infusion Rates

...amycin phosphate must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg per mL. Infusion rates should not exceed 30 mg per minute. The usual infusion dilutions and rates are as follows:

Dose	Diluent	Time
300 mg	50 mL	10 min
600 mg	50 mL	20 min
900 mg	100 mL	30 min
1200 mg	100 mL	40 min

...inistration of more than 1200 mg in a single 1-hour infusion is not recommended.

...ental drug products should be inspected visually for ...ulate matter and discoloration prior to administration, ...ever solution and container permit.

...ion and Compatibility: Physical and biological compatibility studies monitored for 24 hours at room temperature ...demonstrated no inactivation or incompatibility with ...ed CLEOCIN PHOSPHATE Sterile Solution (clindamycin phosphate) in IV solutions containing sodium chloride, dextrose, calcium or potassium, and solutions containing ...B complex in concentrations usually used clinically. ...ompatibility has been demonstrated with the antibiotics ...ptothin, kanamycin, gentamicin, penicillin or carbenicillin.

...following drugs are physically incompatible with clindamycin phosphate: ampicillin sodium, phenytoin sodium, ...barates, aminophylline, calcium gluconate, and magnesium sulfate.

...ompatibility and duration of stability of drug admixtures will vary depending on concentration and other conditions. For current information regarding compatibilities of clindamycin phosphate under specific conditions, please contact the Medical Correspondence Unit, The Upjohn Company.

...Chemical Stability of diluted solutions of CLEOCIN ...ure: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in dextrose 5% in water, sodium chloride 0.9%, ...ted Ringers in glass bottles or minibags, demonstrated physical and chemical stability for at least 16 days at 5°C. Also, 18 mg/mL (equivalent to clindamycin base) in dextrose 5% in water, in minibags, demonstrated physical and chemical stability for at least 16 days at 25°C.

Refrigeration: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in dextrose 5% in water, sodium chloride 0.9%, or Lactated Ringers in glass bottles or minibags, demonstrated physical and chemical stability for at least 32 days at 4°C.

Frozen: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in dextrose 5% in water, sodium chloride 0.9%, or Lactated Ringers in minibags demonstrated physical and chemical stability for at least eight weeks at −10°C.

Frozen solutions should be thawed at room temperature and not refrozen.

DIRECTIONS FOR DISPENSING:

Pharmacy Bulk Package—Not for Direct Infusion

The Pharmacy Bulk Package is for use in a Pharmacy Admixture Service only under a laminar flow hood. Entry into the vial should be made with a small diameter sterile transfer set or other small diameter sterile dispensing device, and contents dispensed in aliquots using aseptic technique. Multiple entries with a needle and syringe are not recommended. AFTER ENTRY USE ENTIRE CONTENTS OF VIAL PROMPTLY. ANY UNUSED PORTION MUST BE DISCARDED WITHIN 24 HOURS AFTER INITIAL ENTRY.

DIRECTIONS FOR USE

CLEOCIN PHOSPHATE IV Solution in Galaxy Plastic Container

Premixed CLEOCIN PHOSPHATE IV Solution is for intravenous administration using sterile equipment. Check for minute leaks prior to use by squeezing bag firmly. If leaks are found, discard solution as sterility may be impaired. Do not add supplementary medication. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use unless solution is clear and seal is intact.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

Preparation of CLEOCIN PHOSPHATE in ADD-Vantage® System-For IV Use Only. CLEOCIN PHOSPHATE 600 mg and 900 mg may be reconstituted in 50 ml or 100 ml, respectively, of 5% Dextrose or 0.9% Sodium Chloride in the ADD-diluent container. Refer to separate instructions for ADD-Vantage System.

HOW SUPPLIED

Each ml of CLEOCIN PHOSPHATE Sterile Solution contains clindamycin phosphate equivalent to 150 mg clindamycin; 0.5 mg disodium edetate; 9.45 mg benzyl alcohol added as preservative. When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid.

CLEOCIN PHOSPHATE is available in the following packages:

25-2 mL vials	NDC 0009-0870-21
25-4 mL vials	NDC 0009-0775-20
25-6 mL vials	NDC 0009-0902-11
1-60 mL Pharmacy Bulk Package	NDC 0009-0728-05

CLEOCIN PHOSPHATE is supplied in ADD-Vantage vials as follows:

NDC#	Vial Size	Total Clindamycin Phosphate/vial	Amount of Diluent
0009-3124-01	4 mL	600 mg	50 mL
0009-3447-01	6 mL	900 mg	100 mL

Store at controlled room temperature 15°-30°C (59°-86°F).

CLEOCIN PHOSPHATE IV Solution in Galaxy plastic containers is a sterile solution of clindamycin phosphate with 5% dextrose. The single dose Galaxy plastic containers are available as follows:

24—300 mg/50 mL containers	NDC 0009-3381-01
24—600 mg/50 mL containers	NDC 0009-3375-01
24—900 mg/50 mL containers	NDC 0009-3382-01

Exposure of pharmaceutical products to heat should be minimized. It is recommended that Galaxy plastic containers be stored at room temperature (25° C). Avoid temperatures above 30° C.

Code 810 020 127

CLEOCIN PHOSPHATE IV Solution in the Galaxy plastic containers is manufactured for The Upjohn Company by Baxter-Healthcare Corporation, Deerfield, IL 60015.

Galaxy© is a registered trademark of Baxter International, Inc.

Shown in Product Identification Section, page 434

CLEOCIN T® **B**

brand of clindamycin phosphate topical solution, topical gel and topical lotion

For External Use

30 mL bottle
NSN 6505-01-140-6450 (M)
60 mL bottle
NSN 6505-01-116-5855 (M & VA)

DESCRIPTION

CLEOCIN T Topical Solution , CLEOCIN T Topical Gel and CLEOCIN T Topical Lotion contain clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per milliliter.

Clindamycin phosphate is a water soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

The solution contains isopropyl alcohol 50% v/v, propylene glycol, and water.

The gel contains allantoin, carbomer 934P, methylparaben, polyethylene glycol 400, propylene glycol, sodium hydroxide, and purified water.

The lotion contains cetostearyl alcohol (2.5%); glycerin; glyceryl stearate SE (with potassium monostearate); isostearyl alcohol (2.5%); methylparaben (0.3%); sodium lauroyl sarcosinate; stearic acid; and purified water.

The chemical name for clindamycin phosphate is 7(S)-chloro-7-deoxylincomycin-2-phosphate. (MW = 504.96.)

CLINICAL PHARMACOLOGY

Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Clindamycin has been shown to have *in vivo* activity against isolates of *Propionibacterium acnes*. This may account for its usefulness in acne.

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

Following multiple topical applications of clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per mL in an isopropyl alcohol and water solution, very low levels of clindamycin are present in the serum (0–3 ng/mL) and less than 0.2% of the dose is recovered in urine as clindamycin.

Clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of CLEOCIN T Topical Solution for 4 weeks was 597 mcg/g of comedonal material (range 0–1490). Clindamycin *in vitro* inhibits all *Propionibacterium acnes* cultures tested (MICs 0.4 mcg/mL). Free fatty acids on the skin surface have been decreased from approximately 14% to 2% following application of clindamycin.

INDICATIONS AND USAGE

CLEOCIN T Topical Solution, CLEOCIN T Topical Gel and CLEOCIN T Topical Lotion are indicated 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

CLEOCIN T Topical Solution, CLEOCIN T Topical Gel and CLEOCIN T Topical Lotion are 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 end fatally. Use of the topical formulation results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported

Continued on next page

Upjohn—Cont.

with the use of topical and systemic clindamycin. Symptoms can occur after a few days, weeks or months following initiation of clindamycin therapy. They have also been observed begin up to several weeks after cessation of therapy with clindamycin. Studies indicate a toxin(s) produced by *Clostridium difficile* 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.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered in cases of severe diarrhea.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil) may prolong and /or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days.

Mild cases of colitis may respond to discontinuance of clindamycin. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered. A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

PRECAUTIONS

CLEOCIN T Topical Solution contains an alcohol base which will cause burning and irritation of the eye. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucous membranes), bathe with copious amounts of cool tap water. The solution has an unpleasant taste and caution should be exercised when applying medication around the mouth.

CLEOCIN T should be prescribed with caution in atopic individuals.

Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin ranging from 100 to 600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to clindamycin. 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 CLEOCIN T. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use

Safety and effectiveness in children under the age of 12 has not been established.

ADVERSE REACTIONS

Skin dryness is the most common adverse reaction seen with the solution.

Clindamycin has been associated with severe colitis which may end fatally (See WARNINGS).

Cases of diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with topical formulations of clindamycin.

Other effects which have been reported in association with the use of topical formulations of clindamycin include:

Local Effects	Systemic Effects
Contact dermatitis	Abdominal pain
Irritation (e.g., erythema, peeling, and burning)	Gastrointestinal disturbances
Oily skin	
Gram-negative folliculitis	

DOSAGE AND ADMINISTRATION

Apply a thin film of CLEOCIN T Topical Solution, CLEOCIN T Topical Lotion or CLEOCIN T Topical Gel twice daily to affected area.

Shake well immediately before using. Keep all dosage form containers tightly closed.

HOW SUPPLIED

CLEOCIN T Topical Solution containing clindamycin phosphate equivalent to 10 mg clindamycin per milliliter is available in the following sizes:

30 mL applicator bottle—NDC 0009-3116-01
60 mL applicator bottle—NDC 0009-3116-02
16 oz (473 mL) bottle—NDC 0009-3116-04

CLEOCIN T Topical Gel containing clindamycin phosphate equivalent to 10 mg clindamycin per milliliter is available in the following sizes:

7.5 gram tube—NDC 0009-3331-03
30 gram tube—NDC 0009-3331-02

CLEOCIN T Topical Lotion containing clindamycin phosphate equivalent to 10 mg clindamycin per milliliter is available in the following size:

60 mL plastic squeeze bottle—NDC 0009-3329-01

Store at controlled room temperature 15°–30°C (59°–86°F). Protect from freezing.

Code 811 373 221

Shown in Product Identification Section, page 434

COLESTID® R

brand of colestipol hydrochloride granules
(colestipol hydrochloride for oral suspension, USP)

Box of 30-5 gram packets NSN 6505-01-051-4697 (M & VA)
Box of 90-5 gram packets NSN 6505-01-292-8929 (M & VA)
300 gram NSN 6505-01-336-6194 (M & VA)
500 gram NSN 6505-01-244-5511 (M & VA)

DESCRIPTION

COLESTID Granules consist of colestipol hydrochloride, which is a lipid lowering agent for oral use. COLESTID is an insoluble, high molecular weight basic anion-exchange copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, with approximately 1 out of 5 amine nitrogens protonated (chloride form). It is a light yellow resin which is hygroscopic and swells when placed in water or aqueous fluids. COLESTID is tasteless and odorless. Inactive ingredient: Silicon dioxide.

CLINICAL PHARMACOLOGY

Cholesterol is the major, and probably the sole precursor of bile acids. During normal digestion, bile acids are secreted via the bile from the liver and gall bladder into the intestines. Bile acids emulsify the fat and lipid materials present in food, thus facilitating absorption. A major portion of the bile acids secreted is reabsorbed from the intestines and returned via the portal circulation to the liver, thus completing the enterohepatic cycle. Only very small amounts of bile acids are found in normal serum.

COLESTID Granules (colestipol hydrochloride) bind bile acids in the intestine forming a complex that is excreted in the feces. This nonsystemic action results in a partial removal of the bile acids from the enterohepatic circulation, preventing their reabsorption. Since colestipol hydrochloride is an anion exchange resin, the chloride anions of the resin can be replaced by other anions, usually those with a greater affinity for the resin than chloride ion.

Colestipol hydrochloride is hydrophilic, but it is virtually water insoluble (99.75%) and it is not hydrolyzed by digestive enzymes. The high molecular weight polymer in COLESTID apparently is not absorbed. Less than 0.05% of ^{14}C-labeled colestipol hydrochloride is excreted in the urine.

The increased fecal loss of bile acids due to administration of COLESTID leads to an increased oxidation of cholesterol to bile acids. This results in an increase in the number of LDL receptors, increased hepatic uptake of LDL and a decrease in beta lipoprotein or low density lipoprotein serum levels, and a decrease in serum cholesterol levels. Although COLESTID produces an increase in the hepatic synthesis of cholesterol in man, serum cholesterol levels fall.

There is evidence to show that this fall in cholesterol is secondary to an increased rate of cholesterol rich lipoproteins (beta or low density lipoproteins) from the plasma. Serum triglyceride levels may increase or remain unchanged in colestipol treated patients.

The decline in serum cholesterol levels with treatment with COLESTID is usually evident by one month. When COLESTID is discontinued, serum cholesterol levels usually return to baseline levels within one month. Periodic determinations of serum cholesterol levels as outlined in the National Cholesterol Education Program (NCEP) guidelines should be done to confirm a favorable initial and long-term response.[1]

In patients with heterozygous familial hypercholesterolemia who have not obtained an optimal response to colestipol hydrochloride alone in maximal doses, the combination of colestipol hydrochloride and nicotinic acid has been shown to provide effective further lowering of serum cholesterol, triglyceride, and LDL cholesterol values. Simultaneously, HDL cholesterol values increased significantly. In many such patients it is possible to normalize serum lipid values.[2-3]

Preliminary evidence suggests that the cholesterol-lowering effects of lovastatin and the bile acid sequestrant, colestipol, are additive.

The effect of intensive lipid-lowering therapy on coronary atherosclerosis has been assessed by arteriography in hypercholesterolemic patients. In these randomized, controlled clinical trials, patients were treated for two to four years by either conventional measures (diet, placebo, or in some cases low dose resin), or with intensive combination therapy using diet plus COLESTID Granules plus either nicotinic acid or lovastatin. When compared to conventional measures, intensive lipid-lowering combination therapy significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions in patients with or at risk for coronary artery disease.[4-6]

INDICATIONS AND USAGE

Since no drug is innocuous, strict attention should be paid to the indications and contraindications, particularly when selecting drugs for chronic long-term use.

COLESTID Granules (colestipol hydrochloride) are indicated as adjunctive therapy to diet for the reduction of elevated serum total and low-density lipoprotein (LDL) cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins [LDL] cholesterol) who do not respond adequately to diet. Generally, COLESTID has no clinically significant effect on serum triglycerides, but with its use triglyceride levels may be raised in some patients.

In a large, placebo-controlled, multiclinic study, the LRC-CPPT[4], hypercholesterolemic subjects treated with cholestyramine, a bile acid sequestrant with a mechanism of action and an effect on serum cholesterol similar to that of COLESTID, had reductions in total and low-density lipoprotein cholesterol (LDL-C). Over the seven-year study period the cholestyramine group experienced a 19% reduction in the combined rate of coronary heart disease death plus non-fatal myocardial infarction (cumulative incidences of 7% cholestyramine and 8.6% placebo). The subjects included in the study were middle-aged men (age 35-59) with serum cholesterol levels above 265 mg/dl, LDL-C above 175 mg/dl on a moderate cholesterol lowering diet, and no history of heart disease. It is not clear to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.

Treatment for elevated serum cholesterol (> 200 mg/dL) should begin with dietary therapy and be carried out in two steps (i.e., Step-One and Step-Two Diets). A minimum of six months of intensive dietary therapy and counseling should be carried out prior to initiation of drug therapy. Shorter periods can be considered in patients with severe elevations of LDL-cholesterol (> 225 mg/dL) or with definite CHD.

CONTRAINDICATIONS

COLESTID Granules (colestipol hydrochloride) are contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS

TO AVOID ACCIDENTAL INHALATION OR ESOPHAGEAL DISTRESS, COLESTID GRANULES (colestipol hydrochloride) SHOULD NOT BE TAKEN IN ITS DRY FORM. ALWAYS MIX COLESTID WITH WATER OR OTHER FLUIDS BEFORE INGESTING.

PRECAUTIONS

Before instituting therapy with COLESTID Granules (colestipol hydrochloride), diseases contributing to increased blood cholesterol such as hypothyroidism, diabetes mellitus, nephrotic syndrome, dysproteinemias and obstructive liver disease should be looked for and specifically treated. The patient's current medications should be reviewed for their potential to increase serum LDL-cholesterol or total cholesterol. It should be verified that an elevated LDL-C level is responsible for high total cholesterol, especially in those patients with marked elevations of high density lipoprotein (HDL) cholesterol and those with triglycerides over 400 mg/dL whose total cholesterol elevation may be due to very low density lipoprotein (VLDL) cholesterol rather than LDL-C.

In most patients, LDL-C may be estimated according to the following equation:

LDL-C = total cholesterol − [0.16 × (triglycerides) + HDL-C]

When the total triglycerides are greater than 400, this equation is less accurate.

Because it sequesters bile acids, COLESTID may interfere with normal fat absorption and thus may prevent absorption of fat soluble vitamins such as A, D, and K.

Chronic use of COLESTID may be associated with an increased bleeding tendency due to hypoprothrombinemia from vitamin K deficiency. This will usually respond promptly to parenteral vitamin K_1 and recurrences can be prevented by oral administration of vitamin K_1.

Serum cholesterol and triglyceride levels should be determined periodically based on NCEP guidelines to confirm a favorable initial and adequate long-term response.

COLESTID may produce or severely worsen pre-existing constipation. The dosage should be increased gradually as tolerated by patients to minimize the risk of developing fecal impaction. In patients with preexisting constipation, the starting dose should be 5 grams (1 packet or 1 scoop) once daily for 1-2

formulation

Redacted 4

Page(s) of trade secret and /or confidential commercial information

E L E C T R O N I C M A I L M E S S A G E

Date: 03-Jan-1997 03:19pm EST
From: Jason Gross
GROSSJ
Dept: HFD-615 MPN2 113
Tel No: 301-594-2290 FAX 301-594-0181

TO: Maria Shih (SHIH)

CC: John Harrison (HARRISONJ)
CC: Mark Anderson (ANDERSONM)

BCC: Robert West (WESTR)

Subject: clindamycin

RE: AADA 64-159, Clindamvcin Top Sol, Fougeria, EER-UN-12-30-96

AADA 64-187, Clindamycin Top Sol, Altana EER-AC-01-02-97

Maria:

As you know the EER for AADA 64-159 was "UN"because of issues with , and the application is with Florence for review before we issue a letter. However we just received an AC-EER for AADA 64-187 which , Since Fougeria and Altana are the same firm it seems strange that they are but its very possible),

two issues:

1. During your review lets make sure that , is not an for AADA 64-187

2. For AADA 64-159, maybe we can get the firm to WD as the , and use though this may have some problems since was used in the Bio-study.

fyi
JAG

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

FILE
Div

REQUEST TYPE *(Check One)*	DATE August 28, 1995	PHONE NO.	EER ID #
REQUESTORS NAME:	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-643
APPLICATION AND SUPPLEMENT NUMBER: ANDA 64-159			
BRAND NAME:	ESTABLISHED NAME: Clindamycin Phopshate Topical Solution		
DOSAGE STRENGTH: 1 % solution in 30 ml and 60 ml		STERILE ☐Yes ☒ No	
PROFILE CLASS:: LIQ	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)* "ready for approval"		
APPLICANT'S NAME: E.Fougera & Co.			
APPLICANT'S ADDRESS: 60 Baylis Road Melville, NY 11747			
COMMENTS : Facility #4 added 12/3/96, firm added facility in 10/30/96 "AC"			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY	
1. Altana Inc. E.Fougera 60 Baylis Melville, NY 11747 2432435	testing	NEC		AC	8/23/96
Altana Inc. 55 Cantiague Rock Road Hicksville, NY 11802	manufactuer of the finished dosage form	LIQ		AC	8/23/96
3. [ ]				UN	4/18/96
4. [ ]		NEC		AC	6/14/96
5.					

FOR HFD-324 USE ONLY:	CSO [signature]	DATE RECEIVED 12/4/96
	COMPLIANCE STATUS [signature]	DATE 12/30/96

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.
cc: ANDA 64-159 HFD-643/Div File, HFD-617/JWilson, HFD-617/TAmes, HFD-643/JSimmons HFD-643/GJSmith
x:\wpfile\eerforms\64159

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

~~REQUEST TYPE~~ *(Check One)* Original	DATE ~~August 28, 1995~~ March 11, 1996	PHONE NO. 594-0360	EER ID # 9728
REQUESTORS NAME: ~~Maria Shih~~ per requester via	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-643
APPLICATION AND SUPPLEMENT NUMBER: ANDA 64-159			
BRAND NAME: ———	ESTABLISHED NAME: Clindamycin Phopshate Topical Solution		
DOSAGE STRENGTH: 1 % solution in 30 ml and 60 ml		STERILE ☐Yes	☒ No
PROFILE CLASS:: LIQ	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*		
APPLICANT'S NAME: E.Fougera & Co.			
APPLICANT'S ADDRESS: 60 Baylis Road Melville, NY 11747			
COMMENTS :			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY ~	
1. Altana Inc. 60 Baylis Melville, NY 11747	testing	LIQ	23875 ALTM	AC	8/23/96
2. Altana Inc. 55 Cantiague Rock Road Hicksville, NY 11802	manufactuer of the finished dosage form	LIQ	23876 ALIH	AC	8/23/96
3 [illegible]					11/8/96
4.			23712		
5.					

FOR HFD-324 USE ONLY:	CSO Dave Dell	DATE RECEIVED	3/11/96
	CGMP COMPLIANCE STATUS LNacogdoche	DATE	12/5/96

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.
ANDA 64-159 HFD-643/Div File, HFD-617/JWilson, HFD-617/TAmes, HFD-643/JSimmons HFD-643/GJSmith
\eerforms\64159

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

FOUGERA
60 BAYLIS RD
MELVILLE NY 11747

AADA N064159

Dear Sir/Madam:

We acknowledge the receipt of your Abbreviated Antibiotic Drug Application submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG:
CLINDAMYCIN PHOSPHATE Topical Solution USP, 1%

DATE OF APPLICATION: 10-AUG-95

DATE OF RECEIPT: 11-AUG-95

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the number shown above.

Send representative samples, three times the amount needed to perform all compendial (CFR/USP) tests except pyrogens and sterility tests, from ___ batches along with the respective certificates of analysis and copies of batch records. The exhibit samples should be from batch sizes that are minimally ___ of the maximum production size and manufactured in production equipment. Send the samples to:

FDA/Division of Research and Testing
Attention: Joseph H. Graham, Ph.D. (HFD-473)
Chief, Antimicrobial Drugs Branch
200 C Street, S.W., Room 2002
Washington, D.C. 20204

Send copies of all correspondence regarding the requested samples to the AADA.

We recommend that you send the samples by registered mail/return receipt requested.

Harrison
Random II
HFD-643

Sincerely yours,

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

HFD-473 (Dr. Joseph H. Graham)

CDER Establishment Evaluation Report
for May 30, 1997

Application: ANDA 64159/000
Stamp: 11-AUG-1995 Regulatory Due:
Applicant: FOUGERA
60 BAYLIS RD
MELVILLE, NY 11747

Priority:
Org Code: 600
Action Goal:
District Goal: 11-OCT-1996
Brand Name:
Established Name: CLINDAMYCIN PHOSPHATE
Generic Name:
Dosage Form: SOL (SOLUTION)
Strength: 1% TOPICAL

FDA Contacts: J. GROSS (HFD-324) 301-827-0062 , Project Manager
J. HARRISON (HFD-643) 301-827-5849 , Team Leader

Overall Recommendation:

ACCEPTABLE on 30-MAY-1997 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 15-JAN-1997 by DOLESKI

Establishment: 2410271
ALTANA INC
CANTIAGUE ROCK RD
HICKSVILLE, NY 11802

DMF No:

Profile: LIQ
OAI Status: NONE
Last Milestone: OC RECOMMENDATIO 15-APR-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment: 2432435
ALTANA INC
60 BAYLIS RD
MELVILLE, NY 11747

DMF No:

Profile: NEC
OAI Status: NONE
Last Milestone: OC RECOMMENDATIO 15-JAN-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
FINISHED DOSAGE RELEASE TESTER

Establishment: [redacted]

DMF No:

Profile: NEC
OAI Status: NONE
Last Milestone: OC RECOMMENDATIO 24-DEC-1996
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

Establishment: [redacted]

DMF No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATIO 30-MAY-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-159

CORRESPONDENCE

fougera®
a division of Altana Inc.

516-454-6389

MINOR AMENDMENT

May 8, 1997

NDA ORIG AMENDMENT

Frank O. Holcomb, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Document Control Room, Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: AADA 64-159
Clindamycin Phosphate Topical Solution USP, 1% (base)

Dear Dr. Holcomb:

Reference is made to your communication of February 13, 1997, wherein we were informed that our application for Clindamycin Phosphate Topical Solution was not approvable due to deficiencies in the manufacturing, processing, packaging, etc. of the [redacted]. We were also informed that arrangements were underway for this facility to be re-inspected by the Office of Compliance.

We have been informed by [redacted], that the [redacted] facility was re-inspected by the Office of Compliance from April 28 - May 1, 1997, and that the documentation for [redacted] was also reviewed.

We have included a letter from [redacted] concerning the inspection. They indicated that they received a three point form FDA 483 of which none of the observations were significant.

RECEIVED
MAY 09 1997
GENERIC DRUGS

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-756-7017

We now respectfully request that our application be re-opened, and as a result of [redacted] successful CGMP inspection and the withdrawal of all products utilizing the only other approved generic [redacted], that our application for Clindamycin Phosphate Topical Solution USP, 1% be approved as expeditiously as possible.

If there are any questions, please contact me at (516) 454-7677.

Sincerely,
E. Fougera & Co.,
division of Altana Inc.

Virginia Carman

Virginia Carman
Associate Director
Regulatory Affairs

VC/kmb

C:\GINGER\CLINPHTO.58

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 64-159

E. Fougera & Co.
Division of Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

FEB 13 '97

Dear Madam:

This is in reference to your abbreviated new drug application dated August 10, 1995, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act, for Clindamycin Phosphate Topical Solution USP, 1% (base).

Reference is also made to your amendment dated October 30, 1996.

This application is deficient and, therefore, not approvable under 21 CFR 314.125(b)(13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the [redacted] or holding of the [redacted], by [redacted] comply with current good manufacturing practice (CGMP) regulations.

Our conclusion is based upon the findings revealed during an initial inspection of [redacted] by representatives of the United States Food and Drug Administration during June 1996. This inspection concentrated on related [redacted] in the same facility and using the same equipment as proposed for [redacted]. Upon review of the inspectors' report and observations, we have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time as it can be demonstrated to the Agency that the CGMP-related issues associated with [redacted] have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved. We note that arrangements are currently being made by the Office of Compliance's Foreign Inspection Team (OCFIT) to reinspect the [redacted] facility.

You should amend this application when your have been notified by [redacted] that the CGMP-related issues have been satisfactorily resolved. Your amendment submitted in response to this not approvable letter will be considered as a MINOR AMENDMENT provided that the amendment contains no significant additional information necessary to remedy the CGMP deficiencies or to address concerns identified by the investigators. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT.

Mr. Edwin Rivera, Compliance Officer in the Center's Investigations and Preapproval Compliance Branch (HFD-322)may be contacted at (301) 594-0098, if you have further questions regarding this issue.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

fougera®
a division of Altana Inc.

Federal Express

NDA ORIG AMENDMENT

N/AM

October 30, 1996

RECEIVED
OCT 31
GENERIC DRUGS

Frank O. Holcombe, Jr., Ph.D.
Director, Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, HFD-650
Rockville, MD 20855-2773

Re: AADA 64-159 MINOR AMENDMENT
Clindamycin Phosphate Topical Solution USP, 1%

Dear Dr. Holcombe:

Reference is made to your communication of August 15, 1996, requesting clarification of previously submitted information.

E. Fougera & Co., division of Altana Inc., is herein amending its as yet unapproved application to include responses to the Office's questions. Each of the Office's comments is reiterated below and our comments immediately follow.

1. Comment:
We note that you include the revised specifications for both [redacted] In the original submission only [redacted] was identified as the [redacted] Please clarify.

Response:
We kindly request that the specifications for [redacted] be withdrawn. These were inadvertently submitted. At a later date (post approval) we will supplement the application to include [redacted] is the only [redacted] for which we are currently seeking approval.

Nadine 11-4-96

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-756-7017

2. Comment:

From the submitted stability data, it is noted that under accelerated conditions and when , the for one of the ten samples at the three-month station is . This value exceeds the established limit (each of ten NMT). Please comment.

Response:

The weight loss for one of the ten samples stored at 40° C/75% RH did indeed exceed the established limit of at the three month interval. An investigation of the failing result concluded that the from a loosely closed container. A copy of the investigation report is presented in Attachment 1.

3. Comment:

Please explain in detail the assay procedures for Clindamycin Phosphate potency and for the degradant content of the final product as reported in stability studies.

Response:

The assay procedure for clindamycin phosphate potency and degradation product levels which was used at the initial time point of the stability study was essentially the USP HPLC procedure. , was added to the standard solution so that , the major degradation product of clindamycin phosphate, could be assayed simultaneously. Any other degradation products were assayed against the

The assay method was revised between the one month and two month stability intervals to no longer require the use of an international standard. The internal standard, has a chemical structure which is quite different from that of clindamycin phosphate, its degradation products and related substances. Slight changes in mobile phase composition cause to elute in a different position relative to the other compounds of interest. The chemists running the assay found that too much time was being spent making fine adjustments of the mobile phase composition to ensure correct elution order and lack of interference with the other compounds. After the 18 month stability interval, additional changes were made based on recommendations from the FDA chemist who assisted with the preapproval inspection:

A. The standard solution contains both clindamycin (from the

[redacted]. In order to ensure that the [redacted] is not contributing free clindamycin, a system suitability solution prepared using only [redacted] must demonstrate a lack of detectable [redacted]

B. In order to ensure adequate resolution of potential impurities, a resolution factor of [redacted] is now specified for clindamycin phosphate and [redacted]. (This requirement was taken from the USP assay of Clindamycin Phosphate Gel.) In order to obtain the specified resolution a [redacted] is now recommended instead of an [redacted]

C. Previously, the only reported impurities were degradation products. Related substances are now to be reported along with degradation products. Potential related substances and degradation products are named and listed by relative retention time in the analytical procedure. The in-process, finished product and stability specifications have been changed to additionally note related substances.

The revised specifications, analytical procedures and validations may be found in the following attachments:

Analytical procedures - Attachment 2
Validation of the Assay for: a – Clindamycin Phosphate, [redacted]
Other Degradation Products and Related Substances - Attachment 3
b - [redacted] - Attachment 4
In process specifications - Attachment 5
Finished product specifications - Attachment 6
Stability specifications - Attachment 7

Saw on 7/2/96 submission

In addition, we request that you send 6 sealed containers of the drug product manufactured from batch # 6448 to the following address for analysis by our laboratory. Each container should contain the appropriate quantity of the drug product as referenced in 21 CFR 453.522 (a). A copy of the Certificate of Analysis should accompany the samples. Please send the samples to:

Food and Drug Administration
Beltsville Research Facility
Attention: Valerie Flournoy (HFD-910)
8501 Muirkirk Road
Laurel, MD 20708
(301) 827-8054

As requested, samples of the drug product have been sent to Ms. Valerie Flournoy (HFD-910) at the Beltsville Research Facility. A copy of the accompanying correspondence is included in Attachment 8.

In addition to the responses to the referenced letter, it was noted during our recent preapproval inspection that we had inadvertently omitted the name of the analytical laboratory which had performed preservative challenge testing on the product. The laboratory is: [redacted] A statement of compliance with the Good Manufacturing Practices is included in Attachment 9.

We also acknowledge that this is a minor amendment.

If there are any additional questions, please contact me at (516) 454-7677 ext. 2091.

Sincerely,
E. Fougera & Co.
a division of Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

VC\ps

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AADA 64-159

E. Fougera & Co.
Division of Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

AUG 15 1996

Dear Madam:

This is in reference to your abbreviated antibiotic application dated August 10, 1995, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Clindamycin Phosphate Topical Solution USP, 1% (base).

Reference is also made to your amendment dated July 2, 1996.

The application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

1. We note that you include the revised specifications for both [redacted]. In the original submission only [redacted] was identified as the [redacted] Please clarify.

2. From the submitted stability data, it is noted that under accelerated conditions and when [redacted] one of the ten samples at the three-month station is [redacted] This value exceeds the established limit (each of ten NMT [redacted] Please comment.

3. Please explain in detail the assay procedures for Clindamycin Phosphate potency and for the degradant content of the final product as reported in the stability studies.

In addition, we request that you send 6 sealed containers of the drug product manufactured from batch # 6448 to the following address for analysis by our laboratory. Each container should contain the appropriate quantity of the drug product as referenced in 21 CFR 453.522(a). A copy of the Certificate of Analysis should accompany the samples. Please send the samples to:

Food and Drug Administration
Beltsville Research Facility
Attention: Valerie Flournoy (HFD-910)
8501 Muirkirk Road
Laurel, MD 20708
(301) 827-8054

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

fougera®
a division of Altana Inc.

July 2, 1996

Federal Express

ORIG AMENDMENT

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Re: AADA 64-159
Clindamycin Phosphate Topical
Solution USP, 1% (base)
MAJOR AMENDMENT

Dear Mr. Sporn:

Reference is made to a communication of March 15, 1996 from Frank Holcomb, Jr., Ph.D., Director, Division of Chemistry II concerning deficiencies in our application.

Each of your concerns is stated and our response immediately follows:

A. Chemistry Deficiencies

Regarding the controls for the drug substance (1-2):

1. Comment:
Your specification for the active ingredient under "Related substances" is misleading due to the omission of solution (1) and solution (2) (Ref. BP 1993, Volume 1, page 165). Please revise.

Response:
The specifications for the active ingredient have been revised to clarify the Related Substances test specification. The revised specifications R1137.00 [redacted] and R1137A.00 [redacted] are included in Attachment 1.

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-756-7017

2. Comment:
Please identify some of the individual impurities for Clindamycin Phosphate.

Response:
Potential individual impurities of clindamycin phosphate and their HPLC relative retention times (RRT) with respect to clindamycin phosphate are listed below. Retention times were determined by running authentic reference substances. A chromatogram of clindamycin phosphate spiked with the impurities at levels about [redacted] is presented in Attachment 2.

Note that the HPLC conditions are the same for the assay and the determination of related substances

RRT	Compound
[redacted]	[redacted]

3. Comment:
In your "Composition Statement" for the finished product on page 52, please provide an extra column "[redacted]" for each ingredient.

Response:
The composition statement has been revised to include a column reflecting [redacted] for each ingredient. This can be found in Attachment 3.

4. Comment:
On Page 127, the information provided for the Altana, Inc. facility located at 60 Baylis Road does not contain a description of the QC testing areas. Please clarify.

Response:
A revised facility description which includes a description of the QC testing area is included in Attachment 4.

5. Comment:
Please confirm that your intended maximum batch size is [redacted]

Response:
We confirm that the intended maximum production batch size is [redacted]

Regarding the specifications for the finished product:

6. Comment:
A specification for [redacted] should be established. Routine assay of its content should be listed as one of the testing items.

Response:
In-process, finished product and stability specifications for [redacted] have been established. The specifications, revised analytical procedures and validation report for the [redacted] assay are presented in Attachments 5-9.

7. Comment:
Please identify some of the degradation products and related substances listed under "Others". It is recommended that you complete this effort with some of the test chromatograms.

Response:
Potential degradation products and related substances are listed below; HPLC relative retention times (RRT) with respect to clindamycin phosphate are also noted. Retention times were determined by running authentic reference substances. A chromatogram of the gel spiked with the related substances at levels of about [redacted] is presented in Attachment 10.

RRT	COMPOUND
[redacted]	

The major degradation product of clindamycin phosphate is [redacted]
These substances are specifically assayed for in the HPLC procedure.

Regarding stability studies:

8. Comment:
   Please explain why the specification for "Specific Gravity" is different for release and for stability.
   Response:
   The release specifications are tighter than the stability specifications to help ensure that normal changes during the expiry period will not result in test failures.

   Based on the results obtained so far, the specifications for specific gravity can be tightened. The revised in-process, finished product and stability specifications are presented in Attachments 5,6 and 7.

9. Comment:

10. Comment:
    From the submitted stability data collected at accelerated and at controlled room temperature conditions, it is noted that assay values of Clindamycin increase after storage at several test stations. Is this observed increase significant, or is it within experimental variations?

    Response:
    Factors contributing to changes in assay values upon storage are assay variability, degradation, and evaporation of the vehicle leading to concentration of the contents. The overall effect on the drug product is typical and reasonable considering the nature of the vehicle ( ) and the container (HDPE).

11. Comment:
    Regarding Degradation Products and Related Substance, we find the results do not justify the proposed high limits (i.e., for ' and for "Total"). Please comment.

Response:
We agree that the limits are too high based on the results obtained at 25-30°C/60% RH and 40°C/75% RH. We have tightened the stability specification for "[redacted] to [redacted], and the specification for "total" to [redacted] The revised specifications are presented in Attachment 7. Updated stability data can be found in Attachment 11.

B. Labeling Deficiencies

1. CONTAINER: 30 mL and 60 mL

Comments:

a. Relocate "for External Use Only" to the main panel.

b. Include the pH range.

c. Revise "See package..." to read as follows:

Usual Dosage: See package...

Response:
Samples of container labeling (FPL) which incorporate all of the above requests are included in Attachment 12.

2. CARTON

Comments:

a. See comments under CONTAINER.

b. Correct the spelling of "thoroughly" on the side panel under Patient Information.

c. Delete [redacted] which appears after "NDC".

Response:
Samples of carton labeling (FPL) which incorporate all of the above requests are included in Attachment 13.

3. INSERT

Comments:

a. DESCRIPTION

Include the molecular formula.

b. CLINICAL PHARMACOLOGY

i. Delete the second paragraph (

ii. Replace '— with "mL". Revise throughout the insert.

iii. Last paragraph, line 3 - ...Phosphate Topical Solution...

c. WARNINGS

Revise the entire section as follows:

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 cultures 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. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral

and parenteral therapy with clindamycin.

d. PRECAUTIONS

i. Add the following text after the General subsection:

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.

ii. Revise the pregnancy subsection heading as follows:

Pregnancy: Teratogenic Effects:
Pregnancy Category B

iii. Nursing Mothers -

1) First sentence - "use" rather than ' —

2) Delete the third sentence " — . Replace it with "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."

iv. Pediatric Use - ... effectiveness in pediatric patients under the ...

e. ADVERSE REACTIONS

Revise the entire section as follows:

In 18 clinical studies of various formulations of Clindamycin Phosphate Topical solution using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events [see table below].

Number of patients reporting events

Treatment Emergent Adverse Event	Solution	Gel	Lotion
	n=553 (%)	n=148 (%)	n=160 (%)
Burning	62 (11)	15 (10)	17 (11)
Itching	36 (7)	15 (10)	17 (11)
Burning/Itching	60 (11)	# (-)	# (-)
Dryness	105 (19)	34 (23)	29 (18)
Erythema	86 (16)	10 (7)	22 (14)
Oiliness/Oily Skin	8 (1)	26 (18)	12* (10)
Peeling	61 (11)	# (-)	11 (7)

not recorded
* of 126 subjects

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 formulation 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.

f. Add the OVERDOSAGE section.

OVERDOSAGE

Topically applied clindamycin topical solution can be absorbed in sufficient amounts to produce system effects (See WARNINGS)

g. HOW SUPPLIED
   i. Add "protect from freezing."

Comment:
Please revise your labels and labeling, as instructed above, and submit final printed containers labels and carton labeling and draft insert labeling (final print if you prefer).

Response:
Final Printed Labeling for the revised package insert has been included in Attachment 14.

We acknowledge that this response is considered a MAJOR amendment. We trust that the enclosed information will allay the concerns of the Agency concerning the proposed drug product.

If there are any questions, please contact me at 516-454-7677 ext.2091.

Sincerely,
E. Fougera & Co.
division of Altana Inc.

Virginia Carman
Associate Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

VC:ch

C:\GINGER\CLIN.3

AADA 64-159

MAR 2 6 1996

E. Fougera & Co.
Division of Atlanta, Inc.
Attention: Virginia Carman
60 Baylis Road
Melville NY 11747

Dear Madam:

Reference is made to your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act for Clindamycin Phosphate Topical Solution USP, 1%.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA 64-159, Original, DUP Jacket
Division File
Field Copy
HFD-600 Reading File
Letter Out, Bio Acceptable

Endorsements:
Endorsements:

A. Patel 3/27/96
R. Mhatre RMM 3/28
J. Gross

DRAFTED: STM 03/27/96 X:\WPFILE\BIO\FINAL\A64159.APP

APPEARS THIS WAY
ON ORIGINAL

AADA 64-159

E. Fougera & Co.
Division of Altana Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

MAR 15 1996

Dear Madam:

This is in reference to your abbreviated antibiotic application dated August 10, 1995, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Clindamycin Phosphate Topical Solution USP, 1% (base).

Reference is also made to your amendment dated October 2, 1995.

The application is deficient and, therefore, not approvable under Section 507 of the Act for the following reasons:

A. Chemistry Deficiencies:

Regarding the controls for the drug substance (1-2):

1. Your specification for the active ingredient under "Related substances" is misleading due to the omission of solution (1) and solution (2) (Ref. BP 1993, Volume 1, page 165). Please revise.

2. Please identify some of the individual impurities.

3. In your "Composition Statement" for the finished product on page 52, please provide an extra column "[redacted]," for each ingredient.

4. On Page 127, the information provided for the Altana Inc. facility located at 60 Baylis Road does not contain a description of the QC testing areas. Please clarify.

5. Please confirm that your intended maximum batch size is [redacted].

Regarding the specifications for the finished product:

6. A specification for isopropyl alcohol should be established. Routine assay of its content should be listed as one of the testing items.

7. Please identify some of the degradation products and related substances listed under "Others". It is recommended that you complete this effort with some of the test chromatograms.

Regarding stability studies:

8. Please explain why the specification for "Specific Gravity" is different for release and for stability.

9. We note that [redacted] is a determination for stability testing. There is no " [redacted] requirement in the release specifications. Please provide the rationale and significance of this additional specification.

10. From the submitted stability data collected at accelerated and at controlled room temperature conditions, it is noted that assay values of Clindamycin increase after storage at several test stations. Is this observed increase significant, or is it within experimental variations?

11. Regarding Degradation Products and Related Substances, we find the results do not justify the proposed high limits (i.e., [redacted] for " [redacted] and [redacted] for "Total"). Please comment.

B. Labeling Deficiencies

1. CONTAINER: 30 mL and 60 mL

   a. Relocate "for External Use Only" to the main panel.

   b. Include the pH range.

   c. Revise "See package..." to read as follows:

      Usual Dosage: See package...

2. CARTON

   a. See comments under CONTAINER.

   b. Correct the spelling of "thoroughly" on the side panel under Patient Information.

   c. Delete [redacted] which appears after "NDC".

3. INSERT

a. DESCRIPTION

Include the molecular formula.

b. CLINICAL PHARMACOLOGY

i. Delete the second paragraph

ii. Replace [illegible] with "mL". Revise throughout the insert.

iii. Last paragraph, line 3 - ...Phosphate Topical Solution...

c. WARNINGS

Revise the entire section as follows:

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 cultures 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. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 mg to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

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

d. PRECAUTIONS

i. Add the following text after the General subsection:

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.

ii. Revise the pregnancy subsection heading as follows:

Pregnancy: Teratogenic Effects: Pregnancy Category B

iii. Nursing Mothers -

1) First sentence - "use" rather than .

2) Delete the third sentence . Replace it with "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."

iv. Pediatric Use - ... effectiveness in pediatric patients under the...

e. ADVERSE REACTIONS

Revise the entire section as follows:

In 18 clinical studies of various formulations of Clindamycin Phosphate Topical solution using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events [see table below].

Number of patients reporting events

Treatment Emergent Adverse Event	Solution n=553(%)	Gel n=148(%)	Lotion n=160(%)
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Itching	36 (7)	15(10)	17(11)
Burning/Itching	60(11)	#(-)	#(-)
Dryness	105(19)	34(23)	29(18)
Erythema	86(16)	10(7)	22(14)
Oiliness/Oily Skin	8(1)	26(18)	12*(10)
Peeling	61(11)	#(-)	11 (7)

not recorded
* of 126 subjects

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 formulation 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.

f. Add the OVERDOSAGE section

OVERDOSAGE

Topically applied clindamycin topical solution can be absorbed in sufficient amounts to produce system effects (See WARNINGS)

g. HOW SUPPLIED

Add "protect from freezing."

Please revise your labels and labeling, as instructed above, and submit final printed containers labels and carton labeling and draft insert labeling (final print if you prefer).

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

for 3/15/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-159

E.Fougera & Co.
Division of Altana, Inc.
Attention: Virgina Carman
60 Baylis Road
Melville, NY 11747

OCT 18 1995

Dear Madam:

We acknowledge the receipt of your abbreviated antibiotic application submitted pursuant to Section 507 of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated September 26, 1995, and your amendment dated October 2, 1995.

NAME OF DRUG: Clindamycin Phosphate Topical Solution USP, 1 %

DATE OF APPLICATION: August 10, 1995

DATE OF RECEIPT: August 11, 1995

DATE ACCEPTABLE FOR FILING: October 3, 1995

We will correspond with you further after we have completed the review of your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Mark Anderson
Consumer Safety Officer
(301) 594-0360

Sincerely yours,

Jerry Phillips 10/18/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-159

E. Fougera & Co.
Division of Altana, Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

SEP 26 1995

Dear Madam:

Please refer to your abbreviated antibiotic application (AADA) dated August 10, 1995, submitted under Section 507 of the Federal Food, Drug and Cosmetic Act for Clindamycin Phosphate Topical Solution USP, 1 %.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this AADA under 21 CFR 314.101(d)(3) for the following reasons:

> While you have stated that your formulation is qualitatively the same as the reference listed drug, you have failed to provide a side-by-side comparison of the formulation of your proposed drug product with that of the reference listed drug product. You must demonstrate that the proposed drug product is qualitatively and **quantitatively** the same as the reference listed drug product. In addition, if any qualitative or quantitative differences do exist between your proposed drug product and the reference listed drug, you must provide information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(v)]. The information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. ph, osmolarity, tonicity) of the proposed drug product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties.

Thus, it will not be filed as an abbreviated antibiotic application within the meaning of Section 507 of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Harvey Greenberg
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

Jerry Phillips 9/26/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA 64-159
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Actg. Chief 9/7/95 date
HFD-615/HGreenberg, CSO 9/6/95 date
HFD-610/CHoppes, Actg.Chief, LRB 9/7/95 date
HFD-643/JHarrison, Sup.CSO 9/7/95 date
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F/T hrw 9-6-95
AADA Refuse to File!

Redacted 6

Page(s) of trade secret and /or confidential commercial information

ALTANA
Altana Inc.

Memorandum

TO: Clindamycin Phosphate Topical Solution USP, 1% File

DATE: October 2, 1995

FROM: D. Pearce

CC:

SUBJECT: Formulation

Clindamycin Phosphate Topical Solution USP, 1% is qualitatively and quantitatively identical to the reference listed drug product, Upjohn's Cleocin T®.

	Ingredient	Cleocin T	Altana Inc.
1.	Clindamycin (from clindamycin phosphate)	10 mg/ml	10 mg/ml
2.	Isopropyl Alcohol	50% (v/v)	50% (v/v)
3.	Propylene Glycol	[redacted]	[redacted]
4.	Water	q.s.	q.s.

Note that [redacted] clindamycin phosphate in the formula provides precisely 1.00% (w/v) = 10 mg/ml clindamycin. The required amount of clindamycin is described in the CFR, USP, PDR (Upjohn) and the Cleocin T labeling. The amount of clindamycin phosphate equivalent to 1% clindamycin is obtained by multiplying 1% by the molecular weight ratio of the two compounds: 1% x [redacted]. This w/v percent can be converted to w/w percent by dividing by the specific gravity of Cleocin T [redacted] (w/w). (The molecular weights of the two compounds were obtained from the USP and the Merck Index. The specific gravity of Cleocin T was determined in our laboratories.)

Cleocin T labeling and Upjohn's information in the PDR indicate that the level of isopropyl alcohol is 50% (v/v). This was independently confirmed in our laboratories using a [redacted] assay procedure which yielded a value of [redacted]. The midpoint of the USP specification for the specific gravity of isopropyl alcohol is [redacted]. Multiplying this value by 50% (v/v) yields the percent (w/v): [redacted]. Dividing [redacted] (w/v) by the specific gravity of Cleocin T yields the percent (w/w): [redacted] (w/v) / [redacted] = [redacted]

The percent of propylene glycol in Cleocin T was determined by two different methods of assay in our laboratories. Assay by [redacted] for quantitation yielded a value of [redacted] Assay by [redacted] found [redacted] The average is [redacted]. Using the

propylene glycol specific gravity of [redacted] (midpoint of the USP specifications) and the Cleocin T specific gravity, [redacted] (w/v) = [redacted], (v/v) = [redacted], (w/w). It seems most probable that Cleocin T was formulated at [redacted], although formulating at [redacted] is essentially equivalent since the propylene glycol specific gravity is so close to [redacted] We chose [redacted] as our formulation amount. This is equivalent to [redacted] and [redacted].

The formulation is completed with water to q.s. Altana Inc. uses [redacted] Water USP; Upjohn labeling simply shows "water" for Cleocin T. It is not known if Upjohn uses [redacted] water or [redacted] water. If Upjohn uses [redacted] water the Altana product would still be equivalent, but would not reflect the greater variation over time of [redacted] water.

The analyses of Cleocin T as described above are directly reflected in the Altana Inc. formula.

The attachments to this memorandum provide more detailed descriptions and documentation of the formulation work.

David M. Pearce

David M. Pearce
Director of Research and Development

vb

Attachments:

Product Formulation Sheet

Memorandum 5/26/94 - Assay of Upjohn's Cleocin T Topical Solution for Isopropyl Alcohol.

Memorandum 6/2/94 - Assay of Upjohn's Cleocin T Topical Solution and Cleocin T Gel for Propylene Glycol.

Product Development Report 11/17/93.

APPEARS THIS WAY
ON ORIGINAL

fougera
Division of Altana Inc.

OK H Mosley 10/5/95

10/16/95 cp

FEDERAL EXPRESS

October 2, 1995

Mr. Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Metro Park North II, HFD-617 Room 237N
Food and Drug Administration
7500 Standish Place
Rockville, Maryland 20855

NDA ORIG AMENDMENT

Re: AADA 64-159
Clindamycin Phosphate Topical Solution USP, 1%

Dear Mr. Phillips:

Reference is made to your communication of September 26, 1995, indicating the Office of Generic Drugs' reasons for refusing to file our application.

Your letter states:

> While you have stated that your formulation is qualitatively the same as the reference listed drug, you have failed to provide a side-by-side comparison of the formulation of your proposed drug product with that of the reference listed drug product. You must demonstrate that the proposed drug product is qualitatively and **quantitatively** the same as the reference listed drug product. In addition, if any qualitative or quantitative differences do exist between your proposed drug product and the reference listed drug, you must provide the information to demonstrate these differences do not affect the safety of the proposed drug product [21 CFR 314.94(a)(9)(v)]. The information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. ph, osmolarity, tonicity) of the proposed drug product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties.
>
> Thus, it will not be filed as an abbreviated antibiotic application within the meaning of Section 507 of the Act.

We wish to respond that although we acknowledge that we did not list a side by side quantitative comparison between our product and the reference listed product, a qualitative comparison could be found in Section 4.2 and 4.3, pages 0008 and 0009.

RECEIVED
OCT 03 1995
GENERIC DRUGS

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-420-1572

Additionally, the quantitative formulation of Cleocin T was determined analytically, and our product was formulated to be quantitatively identical to it. The development report included this analysis and is located in Section 11.1 beginning on page 0139.

We have included herein the original development report as noted above. This report has been prefaced by a report from the Director of Research and Development stating the quantitative comparison of the two drugs, as well as an explanation of the theory and calculations used to determine the formulation of Cleocin T.

As our product is qualitatively and quantitatively identical to the reference drug Cleocin T, there are no issues regarding the safety of the drug product's formulation.

We therefore request that our application for Clindamycin Phosphate Solution USP, 1% be accepted for filing.

Sincerely,
E. Fougera & Co.
division of Altana Inc.

Virginia Carman

Virginia Carman
Associate Director,
Regulatory Affairs

VC/lae

encl.

C:\MISC\64-159.RES

fougera
Division of Altana Inc.

RTF 12 Months 8/28/95

August 10, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Original Submission
Abbreviated Antibiotic Drug Application
Clindamycin Phosphate Topical Solution USP, 1%

Dear Sir or Madam:

Pursuant to the Regulations contained in 21 CFR §314.94, E. Fougera & Co., division of Altana Inc., is submitting this Abbreviated Antibiotic Drug Application to market a new drug, Clindamycin Phosphate Topical Solution USP, 1%.

The reference listed drug that is the basis for this submission is CLEOCIN T® (NDA 50-537), manufactured by THE UPJOHN CO. The proposed drug, Clindamycin Phosphate Topical Solution USP, 1%, contains the same active ingredient in the same strength and dosage form, has the same indications and usage, and route of administration as the reference listed drug.

The exhibit batch (#6448) included in this application was fully packaged utilizing the 30 mL and 60 mL presentations for which approval is currently requested. The number of units filled of each package size and the disposition of any remaining bulk product are reconciled in the exhibit batch record.

Included in this two (2) volume submission, along with Form FDA 356h, is the required Patent Certification and Exclusivity statements, draft Labeling, Bioequivalence Waiver Request, full Components and Composition statements, Raw Materials controls, description of the Manufacturing Facilities, Manufacturing and Processing instructions, In-Process Controls, Filling and Packaging procedures, information on the Container/Closure System, controls for the Finished Dosage Form, Analytical Methods, Finished Dosage Form Stability, Environmental Impact Analysis statement, Certification Requirements of the Generic Drug Enforcement Act of 1992 and Field Copy Certification.

60 Baylis Road, Melville, N.Y. 11747 1-516-454-6996 Fax: 516-420-1572

All regulatory correspondences related to this Abbreviated New Drug Application should be addressed to:

Virginia Carman
Associate Director,
Regulatory Affairs
E. Fougera & Co.,
division of Altana Inc.
60 Baylis Road
Melville, NY 11747

A certified copy of this application is being sent to the New York District Office under separate cover.

We trust that this submission will meet your approval. Please advise if you require any additional information.

Sincerely,
E. Fougera & Co.,
division of Altana Inc.

Virginia Carman

Virginia Carman
Associate Director,
Regulatory Affairs

VC:ab

Enclosures

ALTANA
Altana Inc.

Memorandum

TO: Clindamycin Solution File

DATE: October 14, 1993

FROM: D. Pearce

CC: M. Parris

SUBJECT: Formulation

The qualitative and quantitative formula for Upjohn's Cleocin T Topical Solution is as follows:

1. Clindamycin phosphate, equivalent to 1% (w/v) clindamycin.
2. Isopropyl alcohol 50% (v/v)
3. Propylene glycol [redacted]
4. Water q.s.

The percentage of clindamycin phosphate to be used will vary slightly depending on the raw material potency. Upjohn's labeling, USP XXII and the 1993 PDR all indicate that the formula requires an amount of clindamycin phosphate equivalent to 1% (w/v) of clindamycin.

The level of isopropyl alcohol, 50% (v/v), was determined directly from information provided by Upjohn in the PDR.

The level of propylene glycol, [redacted], was determined by assay. The actual value found was [redacted] Allowing for a typical assay relative error of [redacted], it seems clear that Upjohn formulated at [redacted]

[redacted] Water is used to q.s. the formula. The final pH of the product is required to be [redacted] according to the USP.

David M. Pearce

David M. Pearce

Reference: GA notebook 20, p. 98.

vb

ALTANA INC.
MEMORANDUM

TO: D. Pearce DATE: 8/13/92

FROM: K. Keane CC: I. Ralske
T. Donnangelo

SUBJECT: Preformulation Investigations

The following products were analyzed for [redacted] content:

Clindamycin Phosphate Gel:

methylparaben [redacted] reference: GA notebook 20 page 96
propylene glycol [redacted] reference: GA notebook 20 page 100

Clindamycin Phosphate Topical Solution:

propylene glycol [redacted] reference: GA notebook 20 page 98

Karin Keane

Redacted 5

Page(s) of trade secret and /or confidential commercial information