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
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Reviews / Information Included in this ANDA Review.

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<td>X</td>
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</table>
APPLICATION NUMBER:

64-159

APPROVAL LETTER
B. 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 (HPD-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,

[Signature]

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

64-159

FINAL PRINTED LABELING
CLINDAMYCIN PHOSPHATE TOPICAL SOLUTION USP, 1%

**Use**

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

Clindamycin Phosphate is a water soluble ester of the semi-synthetic antibacterial produced by a 70% chloro substitution of the 7-hydroxy group of the parent antibiotic, lincomycin.

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

The structural formula is represented below:

![Clindamycin Phosphate Structure](image)

Molecular Formula: C_{12}H_{17}ClN_{2}O_{5}S

Molecular Weight: 504.95

The chemical name for clindamycin phosphate is 7-D(3S)-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.

Drug 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., an in vivo antibacterial activity is seen in the skin area adjacent to the site of application.

Clindamycin activity has been demonstrated in cultures from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of Clindamycin Phosphate Topical Solution for 4 weeks was 0.7 mg/ml. (range 0.2-4.0 mg/ml). Clindamycin in vivo inhibits all Propionibacterium acne cultures tested (MIC 0.4 mg/ml). Free fatty acids on the skin surface have been decreased from approximately 14% to 2%

**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**

Oral 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 trend produced by clindamycin in one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be accompanied with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool cultures for Clostridium difficile and steel 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.

Antispasmodic agents such as diphenoxylate with atropine may prolong and/or worsen the condition.

Vomiting 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. Chlorpheniramine or cetirizine may be used instead.

PRECAUTIONS

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

Chlorhexidine Phosphate should be prescribed with caution in atopic individuals.

Drug Interactions: Chlorhexidine has been shown to have neurovascular blocking properties that may enhance the action of other neurovascular 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 chlorhexidine ranging from 100 to 600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to chlorhexidine. 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 chlorhexidine is excreted in human milk following the use of Chlorhexidine Phosphate. However, orally and parenterally administered chlorhexidine 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 the drug, or to discontinue the 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 Chlorhexidine 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).

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Event</th>
<th>Solution n=553 (%)</th>
<th>Gel n=148 (%)</th>
<th>Lotion n=160 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning</td>
<td>62 (11)</td>
<td>15 (10)</td>
<td>17 (11)</td>
</tr>
<tr>
<td>Itching</td>
<td>81 (15)</td>
<td>16 (11)</td>
<td>17 (11)</td>
</tr>
<tr>
<td>Burning/Itching</td>
<td>81 (15)</td>
<td>8 (13)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>106 (19)</td>
<td>34 (23)</td>
<td>29 (18)</td>
</tr>
<tr>
<td>Erythema</td>
<td>36 (16)</td>
<td>16 (13)</td>
<td>23 (14)</td>
</tr>
<tr>
<td>Irritability/Swelling</td>
<td>8 (11)</td>
<td>26 (18)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Peeling</td>
<td>61 (11)</td>
<td>6 (11)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>* of recorded</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gently and parenterally administered chlorhexidine has been associated with severe cutaneous which may be fatal.

Cases of dermatitis, bloody diarrhea and death (including pseudomembrances colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of chlorhexidine and rarely with topical chlorhexidine (see WARNINGS).

Abdominal pain and gastrointestinal disturbances as well as granulocytopenia have also been reported in association with the use of topical formulations of chlorhexidine.

OVERDOSAGE

Topically applied chlorhexidine topical solution can be absorbed in sufficient amounts to produce systemic effects (see WARNINGS).

DISPOSITION AND ADMINISTRATION

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

Keep container tightly closed.

HOW SUPPLIED

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

30 mL, bottle—NEC 0158-0201-30
60 mL, bottle—NEC 0158-0201-60

Store at controlled room temperature (15°-30°C [59°-86°F]). Protect from freezing. Flash Point 78°F.

CAUTION: Federal law prohibits dispensing without prescription.

E. Fougera & Co.
a division of Altice Inc.
Melville, NY 11747
R3S6
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.

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

60 mL

E. FOUGERA & CO.
a division of Altana Inc.
MELVILLE, NEW YORK 11747
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); Do not freeze.
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.
gp range 4.0-7.0.
Visit Orange: See Package Insert for complete product information.
Lot 220190
1/97

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

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REVIEW OF PROFESSIONAL LABELING CHECK LIST

See check list completed January 24, 1996

<table>
<thead>
<tr>
<th>Applicant's Established Name</th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different name than on acceptance to file letter?</td>
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<tr>
<td>Is this product a USP item? If so, USP supplement in which verification was assured.</td>
<td></td>
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</tr>
<tr>
<td>Is this name different than that used in the Orange Book?</td>
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<tr>
<td>If not USP, has the product name been proposed in the PF?</td>
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</tr>
</tbody>
</table>

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)

| 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 Manufacturer/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 bioequivalency 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:**

---

Primary Reviewer: [Signature]  
7/23/96  
Date

Acting Team Leader: [Signature]  
7/24/96  
Date

cc:  
AADA 64-159  
Division File  
HPD-613/APayne\AVezza  
njg\7\22\96\ x:\new...fougera\ltres\txt\rev\64159ap.txt  
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 "NAME".

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

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Event</th>
<th>Solution n=553(%)</th>
<th>Gel n=148(%)</th>
<th>Lotion n=160(%)</th>
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<tr>
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<td>Itching</td>
<td>36 (7)</td>
<td>15(10)</td>
<td>17(11)</td>
</tr>
<tr>
<td>Burning/Itching</td>
<td>60(11)</td>
<td>#(-)</td>
<td>#(-)</td>
</tr>
</tbody>
</table>
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).
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?
BIOEQUIVALENCE 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 bioequivalence 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 Bioequivalence 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 PTR

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.
cc:
AADA 64-159
HFD-613/Pyane\Choppes
njg/2/26/96/x:\new...fougera\lets&rev\64159nal.1d
Review

APPEARS THIS WAY
ON ORIGINAL
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  12/9/96
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_{2}O_{8}PS  M.Wt. = 504.97

Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threol-a-D-galacto-octopyranoside 2-(dihydrogen phosphate)

APPEARS THIS WAY ON ORIGINAL

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
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) 1% (as clindamycin)

14. POTENCY

15. CHEMICAL NAME AND STRUCTURE

C₁₈H₃₄ClN₂O₆PS  M.Wt.= 504.97

Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrazolidinecarboxamido)-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 solutions. In the original submission only one was identified as the other. Ask Firm to clarify.

Q2. Please identify some of the individual impurities.

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

<table>
<thead>
<tr>
<th>RRT</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
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</table>
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Page(s) of trade

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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_{19}H_{34}ClN_{2}O_{8}PS  M.Wt. = 504.97

Methyl 7-chloro-6,7,8-trIDEOXY-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-a-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 In the original submission only was identified as the Please clarify.

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

Q2. 

A2. 

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. The major degradation products 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 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.


Sample validation: satisfactory 10/30/96.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval recommended (pending EER) 12/5/96

19. REVIEWER: DATE COMPLETED:

Maria C. Shih 12/4/96

Appears this way on original.
Redacted

Page(s) of trade
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confidential
commercial
information
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. Peter BRANCH: 3

INITIAL: A DATE: 12/16/96

BRANCH CHIEF: Dr. R.M. Mhaye BRANCH: 3

INITIAL: RMY DATE: 12/17/96

Acting DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: M. Caluwa DATE: 1/7/97

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: __________________________ DATE: _______________
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.

A.P. Patel
Division of Bioequivalence
Review Branch III

RD Initialed R.M. Mhatre
FT Initialed R.M. Mhatre

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

Table 1

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Reference</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin Phosphate</td>
<td>*Cleocin T</td>
<td>Fougera</td>
</tr>
<tr>
<td></td>
<td>10 mg/ ml</td>
<td>10 mg/ ml</td>
</tr>
<tr>
<td>Isopropyl Alcohol</td>
<td>50% v/v</td>
<td>50% v/v</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water, USP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Page(s) of trade

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commercial

information
TO: Jason Gross
CC: John Harrison
CC: Mark Anderson

Subject: RE: clindamycin

We are trying to have the approval of AADA 64-159 (Clindamycin Topical Solution) because the EER problem with ________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 ____________like their other application 64-184. It is confusing sometimes.

Thanks for your attention.
ELECTRONIC MAIL MESSAGE

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

CC: 6 addressees

Subject: AADA 64-159 - Clindamycin Phosphate -

Edwin:

We currently have AADA 64-159 submitted by Fougera for Clindamycin Phosphate Topical Solution, USP. The is We are also aware of a recent letter you sent to 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

Since your letter did not specifically mention are you able to recommend approval for his application by Fougera is otherwise ready for approval in OGD.

Please advise.

Thanks,

Bob
TO: Robert West

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.

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
TO: Robert West

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... his 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
ELECTRONIC MAIL MESSAGE

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
Clindamycin / Official Monographs

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 C₁₈H₂₃Cl₂N₂O₅S in each mL of the Injection taken by the formula:

\[
\frac{10}{V} \left( \frac{C}{P} \right) (R_2/R_3),
\]

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 C₁₈H₂₃Cl₂N₂O₅S per mg of the USP Clindamycin Phosphate RS, \( V \) is the volume, in mL, of Injection taken, and \( R_2 \) and \( R_3 \) 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 (C₁₈H₂₃Cl₂N₂O₅S).

Packaging and storage—Preserve in tight containers.


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 C₁₈H₂₃Cl₂N₂O₅S in each mL of the Topical Solution taken by the formula:

\[
0.1 \left( \frac{C}{P} \right) (R_2/R_3),
\]

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 (C₁₈H₂₃Cl₂N₂O₅S) per mg, calculated on the anhydrous basis.

Packaging and storage—Preserve in Containers for Sterile Solids as described under Injection (1).


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 (C₁₈H₂₃Cl₂N₂O₅S) 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 μg of clindamycin (C₁₈H₂₃Cl₂N₂O₅S) 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, Crystalinity, and Assay under Clindamycin Phosphate.

Clioquinol

![Clioquinol Structure](image)

C₂₃H₂₈Cl₂NO₅S 305.50
8-Quinolinol, 5-chloro-7-ido-5-Chloro-7-ido-8-quinoilinol [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 C₂₃H₂₈Cl₂NO₅S (the 5-chloro-7-ido-8-quinoilinol 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 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.
Clindamycin Phosphate

\[
\text{C}_{15}\text{H}_{23}\text{CIN}_{3}\text{O}_5\text{S} \quad 504.96
\]

\(\text{L}-\text{threо-α-galactо-Octopyranoside, methyl 7-chloro-6,7,8-tri-deoxy-4\{1-methyl-4-propyl-2-pyrrolidinyl\}pyrrolidino-1-thio-2-(dihydrogen phosphate), (2S,trans)}\)

Methyl 7-chloro-6,7,8-trideoxy-4\{1-methyl-4-propyl-2-pyrrolidinyl\}carboxamido\}1-thio-\text{L}-\text{threо-α-galactо-Octopyranoside 2(dihydrogen phosphate) [24729-96-2].} \]

> Clindamycin Phosphate has a potency equivalent to not less than 758 \(\mu\)g of clindamycin \((\text{C}_{15}\text{H}_{23}\text{CIN}_{3}\text{O}_5\text{S})\) per mg, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.


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 (6211)). **[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 (6211))—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm \(\times\) 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 \(\mu\)L) 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 1.3 for clindamycin phosphate and 1.2 for 4′-hydroxyacetophenone. Calculate the quantity, in mg, of \(\text{C}_{15}\text{H}_{23}\text{CIN}_{3}\text{O}_5\text{S}\) in the portion of Clindamycin Phosphate taken by the formula:

\[
100\text{CP}(R_0/R_S)
\]

in which \(C\) is the concentration, in mg per mL, of USP Clindamycin Phosphate RS in the Standard preparation, \(R\) is the potency, in \(\mu\)g of \(\text{C}_{15}\text{H}_{23}\text{CIN}_{3}\text{O}_5\text{S}\) per mg of the USP Clindamycin Phosphate RS, and \(R_0\) 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 \((\text{C}_{15}\text{H}_{23}\text{CIN}_{3}\text{O}_5\text{S})\).

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


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 \((\text{C}_{15}\text{H}_{23}\text{CIN}_{3}\text{O}_5\text{S})\) 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).
CLEOCIN PHOSPHATE IV Solution in the Galaxy plastic containers is manufactured for The Upjohn Company by Baxter-Healthcare Corporation, Deerfield, IL 60015. Galen® is a registered trademark of Baxter International, Inc.

Shown in Product Identification Section, page 434

CLEOCIN®
brand of clindamycin phosphate topical solution, topical gel and topical solution
For External Use
30 ml. bottle
NSN 6505-01-140-6480 (M)
80 ml. bottle
NSN 6505-01-116-5585 (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 30 mg clindamycin per milliliter.

Clindamycin phosphate is a water soluble ester of the semisynthetic antibiotic produced by a 7-Deoxychloro-7-deoxylinomycin-2-phosphate. The chemical name for clindamycin phosphate is 7-Deoxychloro-7-deoxylinomycin-2-phosphate. (MW = 504.36)

CLINICAL PHARMACOLOGY
Although clindamycin phosphate is inactive in vitro, rapid, intrinsically hydrophilic conversion 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 (0.1-0.5 mg/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 clindamycin activity in extracted comedones after application of CLEOCIN T Topical Solution for 6 weeks was 597 mcg/g of comedonal material (range 0-1490). Clindamycin in vitro inhibits Propionibacterium acne in 15 minutes (MIC 0.4 mcg/mL). Free fatty acids on the skin surface have been decreased from approximately 14% to 5% 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)

CLEOCIN T Topical Solution, CLEOCIN T Topical Gel and CLEOCIN T Topical Lotion are contraindicated in individuals with a history of hypersensitivity to penicillin containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

WARNINGS
GENERAL: locally and parenterally administered clindamycin has been associated with severe colitis which may be fatal. Use of the topical formulation results in the absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea and pseudomembranous colitis (including pseudomembranous colitis) have been reported

Continued on next page

Information on these Upjohn products is based on labeling in effect June 1, 1982. Further information concerning these and other Upjohn products may be obtained by direct inquiry to Medical Information, The Upjohn Company, Kalamazoo, Michigan 49001.
Physicians' Desk Reference®

COLESTID®

brand of colestipol hydrochloride capsules (colestipol hydrochloride for oral suspension, UBP)

Box of 250 mg capsules (NSN 6505-01-225-3745 (M & VA))

Box of 400 mg capsules (NSN 6505-01-282-4292 (M & VA))

300 mg (NSN 6505-01-336-1104 (M & VA))

500 mg (NSN 6505-01-244-5511 (M & VA))

DESCRIPTION

COLESTID Granules consist of colestipol hydrochloride, which is a lipophilic, agent for oral use. COLESTID is a highly hydrophobic, inert adsorbent of dietary bile acids and other lipids, particularly cholesterol, in the small bowel. The effects of COLESTID on serum lipid levels are dosedependent. The drug has no known effects on other aspects of lipid metabolism in the liver, as there is no known effect on cholesterol synthesis or on other enzymes. The mechanism of action of COLESTID is believed to be due to the increase in fecal excretion of bile acids and other lipids, which results in a decrease in the amount of these substances available for reabsorption in the liver, thus leading to a decrease in the production of cholesterol.

CLINICAL PHARMACOLOGY

Cholestyramine is the only active principle of colestipol. During normal intestinal absorption, bile acids are secreted into the biliary system, where they are reabsorbed and returned to the circulation. COLESTID interferes with this process by adsorbing bile acids and other lipids from the intestinal lumen, thereby reducing the amount of these substances available for reabsorption in the liver. The decrease in bile acid reabsorption results in a decrease in the synthesis of cholesterol in the liver, leading to a decrease in serum cholesterol levels. The decrease in cholesterol synthesis is accompanied by an increase in the synthesis of bile acids, which are then excreted in the feces. This results in a decrease in the synthesis of cholesterol in the liver, which is reflected in a decrease in serum cholesterol levels. The decrease in cholesterol synthesis is accompanied by an increase in the synthesis of bile acids, which are then excreted in the feces. This results in a decrease in the synthesis of cholesterol in the liver, which is reflected in a decrease in serum cholesterol levels.

ADVERSE REACTIONS

Skin dryness is the most common adverse reaction seen with the medication. Other rare but serious adverse reactions include a mild increase in transaminase enzymes, pruritus, rash, and anemia. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease. COLESTID should be used with caution in patients with a history of anemia or a history of hepatic disease.
Redacted

Page(s) of trade

secret and /or

confidential

commercial

information
TO: Maria Shih
   ( SHIH )
CC: John Harrison
   ( HARRISONJ )
CC: Mark Anderson
   ( ANDERSONM )
BCC: Robert West
   ( WESTR )

Subject: clindamycin

RE: AADA 64-159, Clindamycin 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.

fyl
JAG
**ESTABLISHMENT EVALUATION REQUEST**

**REQUEST TYPE (Check One):**
- [ ] 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 Phosphate Topical Solution
- [ ] DOSAGE STRENGTH: 1% solution in 30 ml and 60 ml
- [ ] STERILE □ Yes □ No

**PROFILE CLASS:**
- [ ] 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**

<table>
<thead>
<tr>
<th>Name and Complete Address</th>
<th>RESPONSIBILITY</th>
<th>DMF NUMBER/PROFILE CODE</th>
<th>FKEY</th>
<th>CIRTS ID</th>
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<td>1. Altana Inc. 60 Baylis 60 Melville, NY 11747</td>
<td>testing</td>
<td>243243-5</td>
<td>NEC</td>
<td>HFD-324 USE ONLY</td>
</tr>
<tr>
<td>Altana Inc. 55 Cantiague Rock Road Hicksville, NY 11802</td>
<td>manufacturer of the finished dosage form</td>
<td></td>
<td>L4</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
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<td>5.</td>
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**FOR HFD-324 USE ONLY:**
- [ ] CSD
- [ ] DATE RECEIVED 12/4/96
- [ ] COMPLIANCE STATUS: Acceptable
- [ ] DATE 12/30/96

---

**Distribution:** Original and Yellow Copy: HFD-324.
- [ ] cc: ANDA 64-159 HFD-643/Div File, HFD-617/J/Wilson, HFD-617/T/Ames, HFD-643/J/Simmons, HFD-643/G/Smith
- [ ] x:\wpfile\earforms\64159
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
Public Health Service  
FOOD AND DRUG ADMINISTRATION  

**ESTABLISHMENT EVALUATION REQUEST**

**REQUEST TYPE (Check One):**  
- [ ] Original  
- [x] August 28, 1998  
- [ ] Phone No. 534-0360  
- [ ] EER ID # 9728

**APPLICATION AND SUPPLEMENT NUMBER:** ANDA 64-159

**BRAND NAME:**  
- [ ] ESTABLISHED NAME: Clindamycin Phosphate Topical Solution

**DOSE STRENGTH:** 1% solution in 30 ml and 60 ml

**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)*

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<th>Responsibility</th>
<th>DMF Number/Profile Code</th>
<th>FKEY</th>
<th>CIRTS ID</th>
</tr>
</thead>
</table>
| 1. Altana Inc.  
60 Baylis  
Melville, NY 11747 | testing | LIQ 26575 | ALTM AC 8/23/96 |
| 2. Altana Inc.  
55 Cantiague Rock Road  
Hicksville, NY 11802 | manufacturer of the finished dosage form | LIQ 26576 | ALTH AC 8/23/96 |
| 3. | | | | |
| 4. | | | | |
| 5. | | | | |

**FOR HFD-324 USE ONLY:**

- [ ] Cassette
- [ ] Date Received: 3/11/96

**COMPLIANCE STATUS:**

- [ ] Date: 6/25/96

**RM FDA 3274 (8/92)**  
Distribution: Original and Yellow Copy: HFD-324.  

ANDA 64-159  

**Signatures:**

- [ ] Date of Signature: 3/11/96
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, 1070

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.

Sincerely yours,

[Signature]

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

HFD-473 (Dr. Joseph H. Graham)
### Establishment 1: 2410271

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

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

### Establishment 2: 2432435

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

### Establishment 3

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

---

**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
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64-159

CORRESPONDENCE
MINOR AMENDMENT

May 8, 1997

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 . 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 that the facility was re-inspected by the Office of Compliance from April 28 - May 1, 1997, and that the documentation for was also reviewed.

We have included a letter from 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 a successful CGMP inspection and the withdrawal of all products utilizing the only other approved generic, 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.

[Signature]
Virginia Carman
Associate Director
Regulatory Affairs

VC/kmb
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 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 or holding of the comply with current good manufacturing practice (CGMP) regulations.

Our conclusion is based upon the findings revealed during an initial inspection of representatives of the United States Food and Drug Administration during June 1996. This inspection concentrated on related in the same facility and using the same equipment as proposed for . 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 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 facility.
You should amend this application when you have been notified by 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 (HPD-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
Federal Express

October 30, 1996

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 ____________.
   In the original submission only ____________ was identified as the '__________'. Please clarify.

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

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

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

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, Other Degradation Products and Related Substances - Attachment 3
b - - Attachment 4
In process specifications - Attachment 5
Finished product specifications - Attachment 6
Stability specifications - Attachment 7

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 Flourney (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
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 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 . In the original submission only was identified as the Please clarify.

2. From the submitted stability data, it is noted that under accelerated conditions and when one of the ten samples at the three-month station is . This value exceeds the established limit (each of ten NMT 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
July 2, 1996

Federal Express

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 and R1137A.00 are included in Attachment 1.
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 \( \rightarrow \), is presented in Attachment 2.

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

<table>
<thead>
<tr>
<th>RRT</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. **Comment:**
   In your "Composition Statement" for the finished product on page 52, please provide an extra column \( \rightarrow \) for each ingredient.

   **Response:**
   The composition statement has been revised to include a column reflecting \( \rightarrow \) 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 ____________

   **Response:**
   We confirm that the intended maximum production batch size is ____________

   Regarding the specifications for the finished product:

6. **Comment:**
   A specification for ____________ 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 ____________ have been established. The specifications, revised analytical procedures and validation report for the ____________ 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 ____________ is presented in Attachment 10.

   **RRT** | **COMPOUND**
   --- | ---
   |

   The major degradation product of clindamycin phosphate is ____________
   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 "---" to ---, and the specification for "total" to ---. 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 --- 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 *vivo*. 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

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

# 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
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:

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

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

APPEARS THIS WAY ON ORIGINAL
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 "---" 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:

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 _____ " is a determination for stability testing. There is no " _____ 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., _____ for " _____ and _____ 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 _____ 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].

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<tr>
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* 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 WARNING)

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,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research
E. Fougera & Co.  
Division of Altana, Inc.  
Attention: Virgina Carman  
60 Baylis Road  
Melville, NY 11747  

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

OCT 18 1995
E. Fougera & Co.
Division of Altana, Inc.
Attention: Virginia Carman
60 Baylis Road
Melville, NY 11747

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, osmolality, 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
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 9/1/95
date
HFD-615/HGreenberg, CSO 9/1/95 date
HFD-610/CHoppe, Actg Chief 1/18/95 date
HFD-643/JHarrison, Sup. CSO 9/1/95 date
WP File\A:\rtaada\64159.rtf
F/T hrw 9-6-95
AADA Refuse to File!
Redacted

Page(s) of trade secret and /or confidential commercial information
Clindamycin Phosphate Topical Solution USP, 1% is qualitatively and quantitatively identical to the reference listed drug product, Upjohn's Cleocin T®.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Cleocin T</th>
<th>Altana Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clindamycin (from clindamycin phosphate)</td>
<td>10 mg/ml</td>
<td>10 mg/ml</td>
</tr>
<tr>
<td>2. Isopropyl Alcohol</td>
<td>50% (v/v)</td>
<td>50% (v/v)</td>
</tr>
<tr>
<td>3. Propylene Glycol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Water</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

Note that 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 \( \frac{M_{	ext{clindamycin}}}{M_{	ext{clindamycin phosphate}}} \). This w/v percent can be converted to w/w percent by dividing by the specific gravity of Cleocin T:

\[
\text{w/w} = \frac{\text{w/v}}{\text{specific gravity}}
\]

(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 an assay procedure which yielded a value of \( \frac{M_{	ext{isopropyl alcohol}}}{M_{	ext{Clindamycin phosphate}}} \). The midpoint of the USP specification for the specific gravity of isopropyl alcohol is \( \frac{\text{w/v}}{2} \). Multiplying this value by 50% (v/v) yields the percent (w/v):

\[
\text{percent (w/v)} = \frac{50\%}{2} \times \frac{M_{	ext{isopropyl alcohol}}}{M_{	ext{Clindamycin phosphate}}}
\]

Dividing \( \frac{\text{w/v}}{\text{specific gravity}} \) by the specific gravity of Cleocin T yields the percent (w/w):

\[
\text{percent (w/w)} = \frac{\text{percent (w/v)}}{\text{specific gravity}}
\]

The percent of propylene glycol in Cleocin T was determined by two different methods of assay in our laboratories. Assay by \( \frac{M_{	ext{propylene glycol}}}{M_{	ext{Clindamycin phosphate}}} \) for quantitation yielded a value of \( \text{found} \). Assay by \( \text{found} \) for quantitation yielded a value of \( \text{found} \). The average is \( \text{found} \). Using the
propylene glycol specific gravity of —— (midpoint of the USP specifications) and the Cleocin T specific gravity, —— (w/v) = ——, (v/v) = ——, (w/w). It seems most probable that Cleocin T was formulated at ——, although formulating at —— is essentially equivalent since the propylene glycol specific gravity is so close to ——. We chose —— as our formulation amount. This is equivalent to —— and ——.

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

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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.

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

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.
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
Associate Director,
Regulatory Affairs

VC/lae

encl.

C:\MISC64-159.RES
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.
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  
Associate Director,  
Regulatory Affairs

VC:ab

Enclosures
TO: Clindamycin Solution File  
FROM: D. Pearce  
SUBJECT: Formulation  

DATE: October 14, 1993  
CC: M. Parris  

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
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 was determined by assay. The actual value found was allowing for a typical assay relative error of , it seems clear that Upjohn formulated at

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

David M. Pearce

Reference: GA notebook 20, p. 98.
The following products were analyzed for content:

**Clindamycin Phosphate Gel:**
- methylparaben reference: GA notebook 20 page 96
- propylene glycol reference: GA notebook 20 page 100

**Clindamycin Phosphate Topical Solution:**
- propylene glycol reference: GA notebook 20 page 98
Redacted

Page(s) of trade

secret and /or

confidential

commercial

information