CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64160

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION/MEETING

Firm was called to inform that the practice of mixing the product before taking the analytical sample for stability is not recommended. The firm was requested to collect samples at the crimp, middle and top of the tube for stability testing and report the results individually.

Firm pointed out that this test is done as part of homogeneity. However the specification for homogeneity is 90-110% of mean. Firm was requested to clarify and out line the sampling procedure.

DATE
1/21/2000

ANDA NUMBER
64-160

IND NUMBER

TELECON

INITIATED BY
X FDA IN PERSON

PRODUCT NAME
Clindamycin Phosphate Gel USP, 1%

FIRM NAME
Altana

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Virginia Carman

TELEPHONE NUMBER
516 454-7677

SIGNATURE
/S/ 1/21/2000

RECORD OF TELEPHONE CONVERSATION

I called Virginia Carman regarding her 11/9/99 telephone amendment. I explained that regarding the position of their stability samples, we wanted the firm to confirm that in their stability program the tubes will be stored on their sides (in their 11/9/99 amendment they only restate the fact that exhibit batch samples were stored on their sides).

Ms Carman said she (now) understood our concern and will state that all future lots placed on stability will be on their sides and revise the stability protocol accordingly.

A telephone amendment will be sent via Fax with hard copy to application.

V:\firmsam\altana\telecons\64160.003

DATE
11/10/99

APPLICATION NUMBER
64-160

TELECON

INITIATED BY FDA

PRODUCT NAME
Clindamycin Phosphate Gel USP

FIRM NAME
Altana

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Virginia Carman
DRA

TELEPHONE NUMBER
631-454-7677 2091

SIGNATURE
/S/

RECORD OF TELEPHONE CONVERSATION

Maria Shih and I called Virginia Carman at Altana to discuss questions based on Ms. Shih's review of the firm's 10/26/99 FAX amendment.

We had the following questions:

Regarding firm's response to our comment 2, we confirmed that for future stability testing the firm will store tubes on their sides (just as they did for exhibit batch).

Regarding response to our comment 4 pertaining to seal integrity or leak testing results, firm has said leak testing results are included in stability report under "weight loss". Ms.Carman explained they use the wt loss as an indication if there is a leakage.
Ms.Shih asked how wt loss was determined and was told the firm weighs and numbers each tube at time 0 and repeats at intervals up to 24 months. Ms. Shih commented the data indicate no weight loss for 60 g tubes but there is a small wt loss in the 30 g tubes. She asked that this wt loss be explained.
Ms Carman said she sould be ready with a response by 11/5/99 and will send as a telephone amendment.

She also said the previously requested data diskette which Dr. Fanning has requested for stats consult should be here by end of week

ddds
11/4/99

APPLICATION NUMBER

64-160

TELECON

INITIATED BY FDA

PRODUCT NAME
Clindamycin Topical Gel

FIRM NAME
Altana

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Virginia Carman

TELEPHONE NUMBER

516-454-7677

SIGNATURE /S/

Patent and Exclusivity Search Results from query on 050615 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

DATE: June 27, 1997 Time: 8:00 HFD-650, MPN-II

Subject: Clindamycin Gel, ANDA 64-160

Meeting Type: Telecon

Meeting Chair: Gordon Johnston

Meeting Recorder: Lizzie Sanchez, Pharm.D.

Office of Generic Drugs:

Gordon Johnston, Deputy Director, OGD
Nicholas Fleischer, Ph.D., Director, Division of Bioequivalence
Mary Fanning, M.D., Associate Director for Medical Affairs

Division of Dermatologic and Dental Drug Products:

Jonathan Wilkin, M.D., Director DDDP
Wilson DeCamp, Ph.D., Chemistry Team Leader, DDDP
Denise Cook, Medical Officer, DDDP
Phyllis Huene, Medical Officer, DDDP

Meeting Objective: To discuss Altana's request for a waiver on their clindamycin gel ANDA with the Division of Dermatologic and Dental Drug Products.

Discussions:

1. The firm would have to show that the drug is dissolved and that there is no interaction between the drug and the gellant. The gellant should not have an effect on the stratum corneum.

2. Both products (test and reference) should have identical microscopic structure. The order in which the ingredients are mixed must not affect the biological effect.

3. A solution does not contain a gellant. In a solution, the active ingredient is dissolved, not suspended. Solutions and gels do not have identical properties.

4. The regulations for topical products do not require that the products are Q1 and Q2. However, consistently, the generic drug industry has indicated that the most critical aspect which may affect topical products, is the change of a supplier. Topical products should not differ in inactive ingredients. Several drug companies have changed suppliers for inactive ingredients and had to reformulate their product. The industry agrees that we should increase the regulatory burden on this issue (as per discussion during SUPAC semisolid meeting).

Agreements:

1. It was agreed that a bioequivalence study will be required. A waiver cannot be granted with the limited information provided.

2. A clinical study for acne will be required. The firm may request a teleconference with the Division of Bioequivalence and Dr. Phyllis Huene, from DDDP, to discuss the design of the clinical study. The study will have to look at reduction of inflammatory and/or non-inflammatory lesions, comedonal lesions vs. total lesions, as well as reduction to a minimum number of lesions.

Action Items:

A letter will be drafted to inform the firm of the decision of the Office to require a clinical study. The firm may request a teleconference through OGD with the DDDP to discuss the design of the study, if they choose to conduct the bioequivalence study.

Drafted ALS

6/3/97

MEETING MINUTES

Meeting Date: January 22, 1997 **Time:** 9:15 a.m.

Location: MPN II - Conference Room "B"

Drug Name/AADA #: Clindamycin Phosphate Gel USP, 1%/ 64-160

External Participant: Fougera

Meeting Chair: Gordon Johnston

External Participant Lead: Virginia Carman

Meeting Recorder: Lizzie Sanchez, Pharm.D., Project Manager

FDA Attendees, titles and offices:

Gordon Johnston	Deputy Director, OGD
Rabindra Patnaik, Ph.D.	Acting Dir., Div. of Bioequivalence
Ramakant Mhatre, Ph.D.	Team Leader, DBE
Shrinivas Nerurkar, Ph.D.	Team Leader, DBE
Yih Chain Huang, Ph.D.	Team Leader, DBE
Man Kochhar, Ph.D.	Reviewer, DBE
Moo Park, Ph.D.	Reviewer, DBE
John Harrison	Team Leader, Chemistry II
Maria Shih	Reviewer, Chemistry II
Don Hare	Special Assistant to Director, OGD

Fougera Attendees:

Steven Brown, R.Ph.	Director, Regulatory Affairs
Virginia Carman	Assoc. Director, Regulatory Affairs
Marcy Adrian	Vice-President
David Pearce	Director, Product Development
Joel Zatz, Ph.D.	Consultant, Rutgers University

Meeting Objectives:

The meeting was held to discuss Fougera's (a division of Altana) position that Clindamycin gel as a single phase gel, behaves similar to a solution. Therefore, a waiver should be granted. FDA had denied a waiver request on a letter dated June 6, 1996. A meeting request was also denied on a letter dated October 9, 1996.

Discussion Points:

1. Virginia Carman discussed 320.22(b)(3) which states that a product is eligible for a waiver if it is a solution for application to the skin, an oral solution, elixir, syrup, tincture or similar **other solubilized form.** It must also contain the same active ingredient and no change in inactive ingredients or other change in the formulation. The firm believes its product meets all of these requirements. She also pointed out that erythromycin gel (Erygel) did not require a bioequivalence study, which was approved 10 months later than clindamycin gel in 1987.

2. David Pierce described the firm's formulation as well as the production process. He showed rheograms to demonstrate no differences in viscosity between the Fougera product and the reference listed drug (RLD), UpJohn's Cleocin T. He also described formulas to show in vitro release rates of both products. Using a non-parametric test, the 90% confidence interval for the ratio of the *in vitro* rate median of the Altana gel to the UpJohn's gel is % to %. This range meets the suggested range for demonstrating equivalence of two semisolids (%). He established that the two formulations are qualitatively and quantitatively the same.

3. Dr. Zatz defined gels. Gels are semisolid formulations based on three dimensional network of molecules or particles; frequently with a high liquid content. There are different types of polymers, used as gelling agents. The amount of polymeric agent in this product is very small %), allowing complete movement and no restraints. He showed in his handout, that the diffusion coefficient in polymer gels is basically the same at different concentrations (within % difference). Transport is the same for gels and solutions if they have the same composition except for the gelling agent. He cited one reference (J. Pharm. Sci., 67, 789 (1978)), which demonstrated that changes of critical components can make a difference in permeability. He showed data comparing the release rates of Fougera's and the RLD products, which were very similar.

4. Dr. Zatz concluded that in the absence of specific binding, the diffusion coefficient of a dissolved drug in a simple gel is essentially the same as in the solution used to form the gel. The release and skin penetration depend on solvent composition. The skin penetration flux from solutions and comparable simple gels, in the absence of specific binding, are identical. There is no difference in *in vitro* release rate between the Fougera's product and the RLD.

5. Dr. Zatz's recommendation is that single phase gels should be considered bioequivalent if the products are Q_1 and Q_2 to the RLD, contain % of a gelling agent and the drug and gelling agent are soluble. He defined Q_2 differences as greater than %. It is the firm's opinion that Fougera's clindamycin gel satisfies all these conditions and demonstrates identical release characteristics as the RLD.

6. Discussion/FDA Comments:

- OGD expressed their dilemma on two issues: scientific and regulatory. On the scientific aspect, in addition to theoretical and physicochemical considerations, there has to be *in vivo* data to support the concept that gels are true solutions. Would skin penetration data (such as skin stripping) provide the evidence for pharmaceutical equivalency to be considered on a global scale within the Agency?

- In vitro/in vivo correlations may need to be developed to establish bioequivalency. Scientific evidence is needed to address rate of diffusion, since gels form a thin film on the skin. Will the two products form the same type of film? Dr. Zatz thinks that the two products will form the same type of film, since they have the same components. Fougera acknowledged the lack of *in vivo* data.

- On the regulatory aspect: can this information on single phase gels be applied to other gels? Fougera believes it can since single phase gels are a small spectrum within the topical formulations.

- A waiver policy will have to be developed. Mr. Johnston pointed out that innovator companies may question generic manufacturers assay methodology and reverse engineering. Dr. Zatz explained that assays for gels are easier than for other formulations. He explained that certain ingredients are likely to be influential in establishing bioequivalency (e.g., surfactants). In vitro skin penetration tests under realistic conditions may be performed by the company or other neutral party.

- A database will be needed. Since polymer mixtures differ from batch to batch, a rheology test may be considered to show that the structures are the same. Viscosity profiles will have to be the same to deem the two products bioequivalent.

- -Film formation will have to be addressed, allowing films to form and measuring the dynamic properties of the film or performing skin penetration tests (in excised human skin) or in vitro permeation of human skin.

Decisions (agreements) reached:

Dr. Patnaik stated that when changes in policy are considered, a consensus within the Agency has to be reached. He promised to discuss the issues with the Division of Dermatologic and Dental Products, Dr. Wilkin and others. Additional data may be provided by the company for a better determination regarding any policy changes. A deadline was not agreed upon.

Unresolved issues or issues requiring further discussion:

None

Signature, minutes preparer: /S/

Concurrence Chair: /S/

Attachments:

RECORD OF TELEPHONE CONVERSATION/MEETING

I called Virginia Carmen about the meeting request she sent to discuss the Div of Bioequivalence's refusal to grant a waiver of in vivo bioequivalence for Clindamycin Gel.

I said we would not be able to make a decision to meet without having a data package to review. I suggested she send the package as part of a new request for a meeting. I said we would consider this outside the scope of the application. If we decide a meeting is warrented, we will set it up. If evidence is determined to be scientifically valid, the firm could then make a formal submission to the application which will be reviewed in turn.

Ms. Carmen thanked me for the information and said she would prepare a submission in the next few days.

Plan: Cancel current meeting request due to insufficient information being submitted to determine whether a meeting is warranted.

DATE
11/15/96

AADA NUMBER
64-160
Bio #96-233

OGD #96-314

IND NUMBER

TELECON

INITIATED BY _ **APPLICANT/ SPONSOR** X **FDA**

MADE X **BY TELE.** _ **IN PERSON**

PRODUCT NAME
Clindamycin Phosphate Gel

FIRM NAME
Fougera/Altana

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Virginia Carman

DRA

TELEPHONE NUMBER
516-454-6996

SIGNATURE
/S/

(this supersedes the approval summary dated 7-24-96)
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 64-160 Date of Submission: April 26, 1999

Applicant's Name: E. Fougera & Co.

Established Name: Clindamycin Phosphate Gel USP, 1% base 30 gram and 60 gram tubes

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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 g and 60 g
30 g - *Satisfactory in FPL as of July 9, 1996 submission.*
60 g - *Satisfactory in FPL as of April 26, 1999 submission.*
Carton Labeling - 1 x 60 mL Satisfactory in FPL as of April 26, 1999 submission 2/7/00
Professional Package Insert Labeling:
Satisfactory in FPL as of April 26, 1999 submission.

Revisions needed post-approval: CRT (see USP); PI – WARNINGS - *Clostridium difficile* and *C. difficile* (*italics*) , OVERDOSAGE - "systemic" rather than "system"

BASIS OF APPROVAL:

Was this approval based upon a petition? NO

What is the RLD on the 356(h) form: Cleocin T Topical Gel, 1%

NDA Number: 50-615

NDA Drug Name: Cleocin T (clindamycin phosphate) Topical Gel, 1%

NDA Firm: UpJohn

Date of Approval of NDA Insert and supplement #: 7/28/94 (S-003)

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: labels on file

Basis of Approval for the Carton Labeling: labeling on file

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.	X		

USP 24			
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? NO Must the package insert accompany the product? YES	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
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)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
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.			X
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?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
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?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	

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.		x	
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?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: PTR: 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.			

FOR THE RECORD:

1. **Review based on the listed drug (Cleocin T Topical Gel, 1% NDA 50-615/S-003 UpJohn, approved 7-28-94).**

2. **There are no patents or exclusivities.**

3. **Package sizes are 7.5 g and 30 g for the innovator and 30 g and 60 g for the generic.**

4. **The inactive ingredients are listed accurately in the DESCRIPTION section.**

5. **Storage/dispensing information:**

   USP: Keep in tight containers.
   ANDA: CRT; Keep container tightly closed.
   NDA: Same.

Date of Review: 10-13-99 **Date of Submission: 4-26-99**

Primary Reviewer: Adolph Vezza /S/ **Date:** 10/14/99

Team Leader: Charlie Hoppes /S/ **Date:** 10/14/99

cc:

ANDA: 64-160
DUP/DIVISION FILE
HFD-613/AVezza/CHoppes (no cc)

Review

"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 9, 1996**

Secondary Reviewer: Angela Payne

AADA Number: 64-160 **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 Gel 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 g submitted July 9, 1996

Carton Labeling: 30 g submitted July 9, 1996

Professional Package Insert Labeling: Submitted July 9, 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: 50-615

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

NDA Firm: Upjohn

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

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

Was this approval based upon an OGD labeling guidance?
No

Basis of Approval for the Container Labels: Cleocin T

Basis of Approval for the Carton Labeling: Cleocin T

Other Comments: Firm will not market the 7.5 g package size at this time.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

See check list completed January 24, 1996

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

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

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

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

/S/
Primary Reviewer

7/23/96
Date

/S/ for
Acting Team Leader
Labeling Review Branch

7/24/96
Date

cc:
AADA 64-160
Division File
HFD-613/APayne\AVezza

review

FILE

HFD-650 and Supplements

M E M O R A N D U M

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

DATE: Decemeber 1, 1995

TO: The File
ANDA 64-160
Clindamycin Phosphate Gel, 1%
E. Fougera
Submission Date: August 11, 1995

FROM: Jason A. Gross, Pharm.D. 12/1/95
CSO, Division of Bioequivalence

To: Keith Chan, Ph.D. 12/4/95
Director,
Division of Bioequivalence

Background:

The firm has asked for a waiver of in vivo bioequivalence for this product. However is not eligible for a waiver. Since it is not a solution. Traditionally we have requested clinical studies.

Proposed Action:

1. Inform the firm by written correspondence (draft letter attached) that the required data is not included and the bioequivalence assessment will not be able to be made without such data.

2. The date of this memo, will be used as the review date of this submission, so that the document can be closed in the comis-system.

3. When the required data is submitted the application will be reviewed per policy.

Rational for letter vs phone call:

It will take time to develop the required data, thus the application will remain open on the bio-review clock though no review can take place until the data is submitted. By sending a written correspondence the document can be closed and then re-opened when the required data is submitted. Thus the firm will be developing the application on our clock.

REVIEW OF PROFESSIONAL LABELING

DIVISION OF LABELING AND PROGRAM SUPPORT

LABELING REVIEW BRANCH

Date of Review: January 24, 1996

Date of Submission: August 11, 1995 and October 4, 1995

Primary Reviewer: Angela M. Payne

AADA Number: 64-160 Review Cycle: #1

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 Gel, 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: 7.5 g and 30 g

a. On the 7.5 g label - Relocate "for External Use Only" so that it appears below the equivalency statement.

b. Include the pH range.

c. We note, the innovator 7.5 gram container is a professional sample size. Do you intend to market this size or is it intended to be used as a professional sample as does the innovator. Please comment and/or revise to include "professional sample" on the label.

2. CARTON

a. See comments under b and c CONTAINER.

b. We encourage you to relocate the "Each gram contains" statement to appear before the storage statement.

3. INSERT

a. DESCRIPTION

i. Include the molecular formula.

ii. First sentence - Clindamycin Phosphate Gel, for topical use, continues...

b. CLINICAL PHARMACOLOGY

i. Delete the second paragraph

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

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 "us".

2) Delete the third sentence
Replace it with "Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

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

e. ADVERSE REACTIONS

Revise the entire section as follows:

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

Number of patients reporting events

Treatment Emergent	Solution	Gel	Lotion

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

not recorded
* of 126 subjects

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

Cases of diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulation of clindamycin and rarely with topical clindamycin (see WARNINGS).

Abdominal pain and gastrointestinal disturbances as well as gram-negative folliculitis have also been reported in association with the use of topical formulations of clindamycin.

f. Add the text to appear as the OVERDOSAGE section following the ADVERSE REACTIONS 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."

ii. Delete the if it is a professional sample size.

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:

The formulation for this product does not contain any alcohol
MSL 2/29/96.

1. Please verify the amount of alcohol calculated.

FOR THE RECORD:

1. Review based on the listed drug (Cleocin T; AADA 50~~537~~515; Upjohn; Appoved February 22, 1994; Revised xxx)

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

3. Package sizes are 7.5 g and 30 g for the innovator and generic.

4. Inactive ingredients are consistent with composition statement on page 60 vol 1.1

5. Storage/Dispensing information:

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

Established Name: Clindamycin Phosphate Gel

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: USP 23

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

Has the product name been proposed in the PF? no

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 60 vol 1.1

Does the product contain alcohol? No

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

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

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

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USP ISSUES: See FTR above

List the USP/NDA/ and ANDA dispensing recommendations: Preserve in tight containers.

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? No

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 above

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

BIOEQUIVALENCY ISSUES: waiver denied 12/6/95.

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

If yes, was a food study performed?

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

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

Date Bioequivalency Study found Acceptable: pending

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

Do you have 12 Final Printed Labels and Labeling? Yes No

If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

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

NDA Number:

NDA Drug Name:

NDA Firm:

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

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

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels:

Basis of Approval for the Carton Labeling:

Other Comments:

PATENT/EXCLUSIVITY ISSUES: SEE FTR

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

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

NOTES/QUESTIONS TO THE CHEMIST: See ABOVE

FOR THE RECORD: SEE above.

/S/ 2/26/96

Primary Reviewer Date

/S/ 2/26/96

Chief, Labeling Rev. Branch Date

cc:

AADA 64-160
HFD-613/APayne\CHoppes

Phillips 2/26/96

Review