CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74873

Trade Name Tretinoin Topical Solution USP, 0.05%

Generic Name Tretinoin Topical Solution USP, 0.05%

Sponsor Copley Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74873

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74873

APPROVAL LETTER

ANDA 74-873

JUN 19 1998

Copley Pharmaceuticals, Inc.
Attention: I. Nudelman
25 John Road
Canton, MA 02021

Dear Sir:

This is in reference to your abbreviated new drug application dated March 27, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Tretinoin Topical Solution USP, 0.05%.

Reference is also made to your amendments dated December 29, 1997; January 19, February 5, May 5, and May 20, 1998.

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 Tretinoin Topical Solution USP, 0.05% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Retin-A Liquid, 0.05% of Johnson and Johnson Consumer Products Inc.).

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 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising,

and Communications (HFD-40). 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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ [redacted] 6/14/01

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74873

FINAL PRINTED LABELING

NDC 38245-655-85

TRETINOIN TOPICAL SOLUTION USP, 0.05%

Contains tretinoin 0.05% by weight and alcohol 55% (denatured with *tert*-butyl alcohol and brucine sulfate). Also contains the inactive ingredients butylated hydroxytoluene and polyethylene glycol 400.

For Topical Use

CAUTION: Federal law prohibits dispensing without prescription.

28 mL

Copley Pharmaceutical, Inc.
Canton, MA 02021

Apply as directed by physician (see package insert).

Warning: Keep out of reach of children.

Store below 30°C (86°F).

LOT: 0001 JUN 10

EXP:

LAB711100

LEA506400

TRETINOIN TOPICAL SOLUTION USP, 0.05% For Topical Use Only

LEA506400

Description: Tretinoin Topical Solution containing tretinoin is used for the topical treatment of acne vulgaris. Tretinoin Topical Solution contains tretinoin 0.05% by weight and alcohol 55% (denatured with *tert*-butyl alcohol and brucine sulfate). Also contains the inactive ingredients butylated hydroxytoluene and polyethylene glycol 400. Chemically, tretinoin is *all-trans*-retinoic acid and has the following structure:

Molecular weight (300.44) and molecular formula ($C_{20}H_{28}O_2$).

CLINICAL PHARMACOLOGY: Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

INDICATIONS AND USAGE: Tretinoin Topical Solution USP, 0.05% is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the long-term use of this product in the treatment of other disorders have not been established.

CONTRAINDICATIONS: Use of the product should be discontinued if hypersensitivity to any of the ingredients is noted.

PRECAUTIONS: *General:* If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of tretinoin, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

Tretinoin preparation for acne treatment should be kept away from the eyes, the mouth, angles of the nose, and mucous membranes. Topical use may induce severe local erythema and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use the medication less frequently, discontinue use temporarily, or discontinue use altogether. Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

Drug Interactions: Concomitant topical medication, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime should be used with caution because of possible interaction with tretinoin. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid with tretinoin. It also is advisable to "rest" a patient's skin until the effects of such preparations subside before use of tretinoin is begun.

Carcinogenesis: Long-term animal studies to determine the carcinogenic potential of tretinoin have not been performed. Studies in hairless albino mice suggest that tretinoin may accelerate the tumorigenic potential of weakly carcinogenic light from a solar simulator. In other studies, when lightly pigmented hairless mice treated with tretinoin were exposed to carcinogenic doses of UVB light, the incidence and rate of development of skin tumors was reduced. Due to significantly different experimental conditions, no strict comparison of these disparate data is possible. Although the significance of these studies to man is not clear, patients should avoid or minimize exposure to sun.

Pregnancy: Teratogenic effects. Pregnancy Category C. Oral tretinoin has been shown to be teratogenic in rats when given in doses 1000 times the topical human dose. Oral tretinoin has been shown to be fetotoxic in rats when given in doses 500 times the topical human dose.

Topical tretinoin has not been shown to be teratogenic in rats and rabbits when given in doses of 100 and 320 times the topical human dose, respectively (assuming a 50 kg adult applies 250 mg of 0.1% cream topically). However, at these topical doses, delayed ossification of a number of bones occurred in both species. These changes may be considered variants of normal development and are usually corrected after weaning. There are no adequate and well-controlled studies in pregnant women. Tretinoin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tretinoin is used by a nursing mother.

TRETINOIN TOPICAL SOLUTION USP, 0.05% PATIENT INSTRUCTIONS Acne Treatment

IMPORTANT

Read Directions Carefully Before Using

For Topical Use Only

THIS LEAFLET TELLS YOU ABOUT TRETINOIN ACNE TREATMENT AS PRESCRIBED BY YOUR PHYSICIAN. THIS PRODUCT IS TO BE USED ONLY ACCORDING TO YOUR DOCTOR'S INSTRUCTIONS, AND IT SHOULD NOT BE APPLIED TO OTHER AREAS OF THE BODY OR TO OTHER GROWTHS OR LESIONS. THE LONG-TERM SAFETY AND EFFECTIVENESS OF THIS PRODUCT IN OTHER DISORDERS HAVE NOT BEEN EVALUATED. IF YOU HAVE ANY QUESTIONS, BE SURE TO ASK YOUR DOCTOR.

WARNINGS AND PRECAUTIONS

The effects of the sun on your skin. As you know, overexposure to natural sunlight or the artificial sunlight of a sunlamp can cause sunburn. Overexposure to the sun over many years may cause premature aging of the skin and even skin cancer. The chances of these effects occurring will vary depending on skin type, the climate and the care taken to avoid overexposure to the sun. Therapy with tretinoin may make your skin more susceptible to sunburn and other adverse effects of the sun, so unprotected exposure to natural or artificial sunlight should be minimized.

Laboratory findings. *When laboratory mice are exposed to artificial sunlight, they often develop skin tumors. These sunlight-induced tumors may appear more quickly and in greater number if the mouse is also topically treated with the active ingredient in tretinoin. In some studies, under different conditions, however, when mice treated with the active ingredient tretinoin were exposed to artificial sunlight, the incidence and rate of development of skin tumors was reduced. There is no evidence to date that tretinoin alone will cause the development of skin tumors in either laboratory animals or humans. However, investigations in this area are continuing.*

Use caution in the sun. When outside, even on hazy days, areas treated with tretinoin should be protected. An effective sunscreen should be used any time you are outside (consult your physician for a recommendation of an SPF level which will provide you with the necessary high level of protection). For extended sun exposure, protective clothing, like a hat, should be worn. Do not use artificial sunlamps while you are using tretinoin. If you do become sunburned, stop your therapy with tretinoin until your skin has recovered.

Avoid excessive exposure to wind or cold. Extremes of climate tend to dry or burn normal skin. Skin treated with tretinoin may be more vulnerable to these extremes. Your physician can recommend ways to manage your acne treatment under such conditions.

Possible problems. The skin of certain sensitive individuals may become excessively red, swollen, blistered or crusted. If you are experiencing severe or persistent irritation, discontinue

the topical human dose, respectively (assuming a 50 kg adult applies 250 mg of 0.1% cream topically). However, at these topical doses, delayed ossification of a number of bones occurred in both species. These changes may be considered variants of normal development and are usually corrected after weaning. There are no adequate and well-controlled studies in pregnant women. Tretinoin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when tretinoin is used by a nursing mother.

TRETINOIN TOPICAL SOLUTION USP, 0.05%
PATIENT INSTRUCTIONS
Acne Treatment

IMPORTANT
Read Directions Carefully Before Using

For Topical Use Only

THIS LEAFLET TELLS YOU ABOUT TRETINOIN ACNE TREATMENT AS PRESCRIBED BY YOUR PHYSICIAN. THIS PRODUCT IS TO BE USED ONLY ACCORDING TO YOUR DOCTOR'S INSTRUCTIONS, AND IT SHOULD NOT BE APPLIED TO OTHER AREAS OF THE BODY OR TO OTHER GROWTHS OR LESIONS. THE LONG-TERM SAFETY AND EFFECTIVENESS OF THIS PRODUCT IN OTHER DISORDERS HAVE NOT BEEN EVALUATED. IF YOU HAVE ANY QUESTIONS, BE SURE TO ASK YOUR DOCTOR.

WARNINGS AND PRECAUTIONS

The effects of the sun on your skin. As you know, overexposure to natural sunlight or the artificial sunlight of a sunlamp can cause sunburn. Overexposure to the sun over many years may cause premature aging of the skin and even skin cancer. The chances of these effects occurring will vary depending on skin type, the climate and the care taken to avoid overexposure to the sun. Therapy with tretinoin may make your skin more susceptible to sunburn and other adverse effects of the sun, so unprotected exposure to natural or artificial sunlight should be minimized.

Laboratory findings. *When laboratory mice are exposed to artificial sunlight, they often develop skin tumors. These sunlight-induced tumors may appear more quickly and in greater number if the mouse is also topically treated with the active ingredient in tretinoin. In some studies, under different conditions, however, when mice treated with the active ingredient tretinoin were exposed to artificial sunlight, the incidence and rate of development of skin tumors was reduced. There is no evidence to date that tretinoin alone will cause the development of skin tumors in either laboratory animals or humans. However, investigations in this area are continuing.*

Use caution in the sun. When outside, even on hazy days, areas treated with tretinoin should be protected. An effective sunscreen should be used any time you are outside (consult your physician for a recommendation of an SPF level which will provide you with the necessary high level of protection). For extended sun exposure, protective clothing, like a hat, should be worn. Do not use artificial sunlamps while you are using tretinoin. If you do become sunburned, stop your therapy with tretinoin until your skin has recovered.

Avoid excessive exposure to wind or cold. Extremes of climate tend to dry or burn normal skin. Skin treated with tretinoin may be more vulnerable to these extremes. Your physician can recommend ways to manage your acne treatment under such conditions.

Possible problems. The skin of certain sensitive individuals may become excessively red, swollen, blistered or crusted. If you are experiencing severe or persistent irritation, discontinue the use of tretinoin and consult your physician.

There have been reports that, in some patients, areas treated with tretinoin developed a temporary increase or decrease in the amount of skin pigment (color) present. The pigment in these areas returned to normal either when the skin was allowed to adjust to tretinoin or therapy was discontinued.

Use other medication only on your physician's advice. Only your physician knows which other medications may be helpful during treatment and will recommend them to you if necessary. Follow the physician's instructions carefully. In addition, you should avoid preparations that may dry or irritate your skin. These preparations may include certain astringents, toiletries containing alcohol, spices or lime, or certain medicated soaps, shampoos and hair permanent solutions. Do not allow anyone else to use this medication.

Do not use other medications with tretinoin which are not recommended by your doctor. The medications you have used in the past might cause unnecessary redness or peeling.

If you are pregnant, think you are pregnant or are nursing an infant: No studies have been conducted in humans to establish the safety of tretinoin in pregnant women. If you are pregnant, think you are pregnant, or are nursing a baby, consult your physician before using this medication.

AND WHILE YOU'RE ON TRETINOIN THERAPY

Use a mild, non-medicated soap. Avoid frequent washings and harsh scrubbing. Acne isn't caused by dirt, so no matter how hard you scrub, you can't wash it away. Washing too frequently or scrubbing too roughly may at times actually make your acne worse. Wash your skin gently with a mild, bland soap. Two or three times a day should be sufficient. Pat skin dry with a towel. Let the face dry 20 to 30 minutes before applying tretinoin. Remember, excessive irritation such as rubbing, too much washing, use of other medications not suggested by your physician, etc., may worsen your acne.

ADVERSE REACTIONS: The skin of certain sensitive individuals may become excessively red, edematous, blistered, or crusted. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the medication should be adjusted to a level the patient can tolerate. True contact allergy to topical tretinoin is rarely encountered. Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin. Some individuals have been reported to have heightened susceptibility to sunlight while under treatment with tretinoin. To date, all adverse effects of tretinoin have been reversible upon discontinuance of therapy (see Dosage and Administration Section).

OVERDOSAGE: If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of vitamin A.

DOSAGE AND ADMINISTRATION: Tretinoin Topical Solution USP, 0.05% should be applied once a day, before retiring, to the skin where acne lesions appear, using enough to cover the entire affected area lightly. Topical Solution: The topical solution may be applied using a fingertip, gauze pad, or cotton swab. If gauze or cotton is employed, care should be taken not to oversaturate it to the extent that the topical solution would run into areas where treatment is not intended.

Application may cause a transitory feeling of warmth or slight stinging. In cases where it has been necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be resumed or frequency of application increased when the patients become able to tolerate the treatment.

Alterations of vehicle, drug concentration, or dose frequency should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance.

During the early weeks of therapy, an *apparent* exacerbation of inflammatory lesions may occur. This is due to the action of the medication on deep, previously unseen lesions and should not be considered a reason to discontinue therapy.

Therapeutic results should be noticed after two to three weeks but more than six weeks of therapy may be required before definite beneficial effects are seen.

Once the acne lesions have responded satisfactorily, it may be possible to maintain the improvement with less frequent applications, or other dosage forms.

Patients treated with tretinoin preparation may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied. **(See Precautions)**

HOW SUPPLIED:

Tretinoin Topical Solution USP, 0.05% is supplied as:

Tretinoin Solution

NDC Code	Tretinoin Strength/Form	Tretinoin Qty.
38245-655-85	0.05% Topical solution	28 mL

Storage Conditions: Store below 30°C (86°F).

Copley Pharmaceutical, Inc.
Canton, MA

Revised: November, 1997
LEA506400
MG #13286

HOW TO USE TRETINOIN

To get the best results with tretinoin therapy, it is necessary to use it properly. Forget about the instructions given for other products and the advice of friends. Just stick to the special plan your doctor has laid out for you and be patient. Remember, when tretinoin is *used properly,* many users see improvement by 12 weeks. AGAIN, FOLLOW INSTRUCTIONS - BE PATIENT - DON'T START AND STOP THERAPY ON YOUR OWN - IF YOU HAVE QUESTIONS, ASK YOUR DOCTOR.

To help you use the medication correctly, keep these simple instructions in mind.

- Apply tretinoin once daily before bedtime, or as directed by your physician. Your physician may advise, especially if your skin is sensitive, that you start your therapy by applying tretinoin every other night. First, wash with a mild soap and dry your skin gently. WAIT 20 to 30 MINUTES BEFORE APPLYING MEDICATION; it is important for skin to be completely dry in order to minimize possible irritation.
- It is better not to use more than the amount suggested by your physician or to apply more frequently than instructed. Too much may irritate the skin, waste medication and won't give faster or better results.
- Keep the medication away from the corners of the nose, mouth, eyes and open wounds. *Spread away from these areas when applying.*

- *Topical Solution:* Tretinoin topical solution may be applied to the skin where acne lesions appear, spreading the medication over the entire affected area, using a fingertip, gauze pad, or cotton swab. If gauze or cotton is employed, care should be taken not to oversaturate it to the extent that the topical solution would run into areas where treatment is not intended (such as corners of the mouth, eyes, and nose).
- It is recommended that you apply a moisturizer or a moisturizer with sunscreen that will not aggravate your acne (noncomedogenic) every morning after you wash.

WHAT TO EXPECT WITH YOUR NEW TREATMENT

Tretinoin works deep inside your skin and this takes time. You cannot make tretinoin work any faster by applying more than one dose each day, but an excess amount of tretinoin may irritate your skin. Be patient.

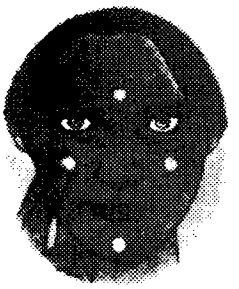
There may be some discomfort or peeling during the early days of treatment. Some patients also notice that their skin begins to take on a blush.

These reactions do not happen to everyone. If they do, it is just your skin adjusting to tretinoin and this usually subsides within two to four weeks. These reactions can usually be minimized by following instructions carefully. Should the effects become excessively troublesome, consult your doctor.

HOW TO USE TRETINOIN

To get the best results with tretinoin therapy, it is necessary to use it properly. Forget about the instructions given for other products and the advice of friends. Just stick to the special plan your doctor has laid out for you and be patient. Remember, when tretinoin is *used properly,* many users see improvement by 12 weeks. AGAIN, FOLLOW INSTRUCTIONS - BE PATIENT - DON'T START AND STOP THERAPY ON YOUR OWN - IF YOU HAVE QUESTIONS, ASK YOUR DOCTOR.

To help you use the medication correctly, keep these simple instructions in mind.



- Apply tretinoin once daily before bedtime, or as directed by your physician. Your physician may advise, especially if your skin is sensitive, that you start your therapy by applying tretinoin every other night. First, wash with a mild soap and dry your skin gently. WAIT 20 to 30 MINUTES BEFORE APPLYING MEDICATION; it is important for skin to be completely dry in order to minimize possible irritation.
- It is better not to use more than the amount suggested by your physician or to apply more frequently than instructed. Too much may irritate the skin, waste medication and won't give faster or better results.
- Keep the medication away from the corners of the nose, mouth, eyes and open wounds. *Spread away from these areas when applying.*
- *Topical Solution:* Tretinoin topical solution may be applied to the skin where acne lesions appear, spreading the medication over the entire affected area, using a fingertip, gauze pad, or cotton swab. If gauze or cotton is employed, care should be taken not to oversaturate it to the extent that the topical solution would run into areas where treatment is not intended (such as corners of the mouth, eyes, and nose).
- It is recommended that you apply a moisturizer or a moisturizer with sunscreen that will not aggravate your acne (noncomedogenic) every morning after you wash.

WHAT TO EXPECT WITH YOUR NEW TREATMENT

Tretinoin works deep inside your skin and this takes time. You cannot make tretinoin work any faster by applying more than one dose each day, but an excess amount of tretinoin may irritate your skin. Be patient.

There may be some discomfort or peeling during the early days of treatment. Some patients also notice that their skin begins to take on a blush.

These reactions do not happen to everyone. If they do, it is just your skin adjusting to tretinoin and this usually subsides within two to four weeks. These reactions can usually be minimized by following instructions carefully. Should the effects become excessively troublesome, consult your doctor.

BY THREE TO SIX WEEKS, some patients notice an appearance of new blemishes (papules and pustules). At this stage, it is *important to continue* using the tretinoin preparation.

If tretinoin is going to have a beneficial effect for you, you should notice a continued improvement in your appearance after 6 to 12 weeks of therapy. Don't be discouraged if you see no immediate improvement. Don't stop treatment at the first signs of improvement.

Once your acne is under control you should continue regular application of tretinoin until your physician instructs otherwise.

IF YOU HAVE QUESTIONS

Refer all questions of a medical nature to your doctor.

Copley Pharmaceutical, Inc.
Canton, MA
Revised: November, 1997
LEA506400
MG #13286

SODIUM DROPS CTN

WARNING!
DO NOT MODIFY DIE LINE

CAR604800

TRETINOIN TOPICAL SOLUTION USP, 0.05%
28 mL
NDC 38245-655-85

Warning: Keep out of reach of children.

Store below 30°C (86°F).

Pharmacist Please Note
The Combined Insert

Unless otherwise instructed by Physician, dispense prescription with Patient Package Insert only. Remove Physician Package Insert at perforation.

Apply as directed by physician (see package insert).

See end flap for lot number and expiration date.

N 3 38245-655-85 4

Copley Pharmaceutical, Inc.
Canton, MA 02021

NDC 38245-655-85

TRETINOIN TOPICAL SOLUTION USP, 0.05%

Contains tretinoin 0.05% by weight and alcohol 55% (denatured with *tert*-butyl alcohol and brucine sulfate). Also contains the inactive ingredients butylated hydroxytoluene and polyethylene glycol 400.

CAUTION: Federal law prohibits dispensing without prescription.

For Topical Use

28 mL

Copley Pharmaceutical, Inc.
Canton, MA 02021

APPROVED

CAR604800

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74873

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-873

3. NAME AND ADDRESS OF APPLICANT

Copley Pharmaceutical, Inc.
25 John Rd
Canton, MA 02021

4. LEGAL BASIS FOR SUBMISSION

The firm certifies that, in their opinion and to the best of their knowledge, there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug. Also indicated that there is no exclusivity period has been granted to Retin-A-Liquid.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Tretinoin

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Original 3/27/96
Amendment 4/18/96
Amendment 12/29/97
Amendment 2/5/98
~~Amendment 5/4/98~~
Amendment 5/5/98
Amendment 5/~~18~~19/98

10. PHARMACOLOGICAL CATEGORY

Treatment of acne vulgaris

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

(b)(4)(CC) [redacted]

13. DOSAGE FORM

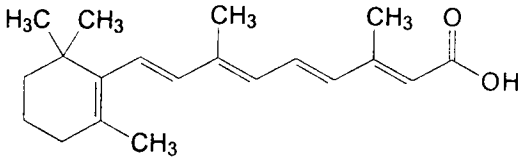
Solution

14. POTENCY

0.05%

15. CHEMICAL NAME AND STRUCTURE

Tretinoin. Retinoic acid. $C_{20}H_{28}O_2$. 300.44. 302-79-4. Keratolytic. USP 23, page 1572.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 5/20/98

Supervisor: Paul Schwartz, Ph.D. 5/20/98

cc: ANDA 74 873
Division File
Field Copy

Endorsements:
HFD-627/N.Nashed, Ph.D./5-20-98 /ISI [redacted] 5/27/98
HFD-627/P.Schwartz, Ph.D./5-20-98 [redacted] 5/28/98
X:\NEW\FIRMSAM\COPLEY\LTRS&REV\74-873.2
F/T by: bc/5-27-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74873

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE
SIGN-OFF FORM

ANDA: 74-873 SPONSOR : Copley Pharmaceutical
DRUG & DOSAGE FORM : Tretinoin Topical Solution USP, 0.05%

TYPE OF STUDY:	SD	SDF	MD	Others
STUDY:	☐Acceptable		XNot Applicable	
DISSOLUTION :	☐Acceptable		XNot Applicable	
WAIVER:	XAcceptable		☐Not Applicable	

REVIEWER: Hoainhon Nguyen BRANCH: I
INITIAL: /S/ [redacted] DATE : 5/18/98

BRANCH CHIEF : Yih-Chain Huang, Ph.D. BRANCH : I
INITIAL : /S/ [redacted] DATE : 5/18/98

DIRECTOR: Dale P. Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE
INITIAL : /S/ [redacted] DATE : 5/19/98

ANDA 74-873

Copley Pharmaceuticals, Inc.
Attention: W.E. Brochu, Ph.D.
25 John Road
Canton Commerce Center
Canton MA 02021

JUL 31 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Tretinoin Topical Solution USP, 0.05%.

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,

/S/ [redacted]

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

JUL 29 1996

Tretinoin Topical Solution USP, 0.05%
ANDA# 74-873
Reviewer: Hoainhon Nguyen
WP # 74873w.396

Copley Pharmaceutical
Canton, MA
Submission Date:
March 27, 1996

Review of Waiver Request

The firm has requested a waiver of in vivo bioavailability requirements for its Tretinoin Topical Solution USP, 0.50%, in accordance with 21 CFR 320.22 (b) (3).

Comments:

1. The test product is a topical solution.

2. The test product contains tretinoin as the active drug ingredient in the same concentration as the RLD product, Retin-A Liquid 0.05%, manufactured by Dermatological Division Ortho Pharmaceutical Corp..

3. The test product contains the same inactive ingredients as the RLD. Comparative formulations of the test and listed drug products are given below: (**NOTE: The formulations are not to be released through FOI**)

Ingredients	Copley's %w/w	Retin-A %w/w
Tretinoin	0.0625*	0.05
Polyethylene Glycol 400 Butylated Hydroxytoluene Alcohol Denatured with tert-Butyl Alcohol and Brucine	(b)(4)(TS) [redacted]	

*Includes a 25% Manufacturing Excess for Product Shelf-Life Expiration Dating

Recommendations:

The Division of Bioequivalence agrees that the information submitted by Copley Pharmaceutical demonstrates that its Tretinoin Topical Solution USP, 0.05%, falls under 21 CFR 320.22 (b) (3) of the Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of in vivo bioavailability study

be granted. The test product is deemed bioequivalent to Retin-A Liquid 0.05% manufactured by Dermatological Division Ortho Pharmaceutical.

/S/ 7/24/96
Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ 7/24/96

Concur: /S/ Date: 7/25/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

Hnguyen/htn/07-16-96/wp#74873w.396

cc: ANDA # 74-873 (original, duplicate), HFD-630, HFD-600(Hare), HFD-652(Huang, Nguyen), Drug File, Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74873

ADMINISTRATIVE DOCUMENTS

APPROVAL PACKAGE SUMMARY FOR 74-873

ANDA: 74-873

FIRM: Copley Pharmaceutical, Inc.

DRUG: Tretinoin

DOSAGE: Solution

STRENGTH: 0.05%

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 3/17/98.

BIO STUDY/BIOEQUIVALENCE STATUS: Bio waiver was granted 7/25/96.

METHODS VALIDATION: The drug product is compendial

STABILITY: The firm has provided three months accelerated stability data at 40°C for 1 oz amber glass bottle in upright position and inverted position. Also submitted 24 months room temperature stability data at 25-30°C in upright and inverted positions. In addition freeze-thaw data was included.

LABELING REVIEW STATUS: Labeling is satisfactory 2/11/98.

STERILIZATION VALIDATION: N/A

BATCH SIZES: The firm has provided the master formula and manufacturing instruction for the scale-up batch (b)(4)(CC) and a copy of the executed batch record for (b)(4)(CC lot # 655Z02. The firm will be using the same drug substance manufacture (b)(4)(CC) The DMF is satisfactory and using the same equipment and manufacturing procedure.

COMMENTS: The application is approvable.

/S/

Reviewer: Nashed E. Nashed, Ph.D. Date: 5/20/98

5/20/98

Supervisor: Paul Schwartz, Ph.D. /S/

X:\NEW\FIRMSAM\COPLEY\LTRS&REV\74-873.SUM

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

ESTABLISHMENT EVALUATION REQUEST

J

REQUEST TYPE *(Check One)* ☒ Original ☐ FollowUp ☐ FUR	DATE April 29, 1996	PHONE NO. (301)594-1841	EER ID # 10091
REQUESTORS NAME: Anna Marie Weikel	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-629
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-873			
BRAND NAME:	ESTABLISHED NAME: Tretinoin Topical Solution		
DOSAGE STRENGTH: 0.05%			STERILE ☐Yes ☒ No
PROFILE CLASS:: LIQ	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*		
APPLICANT'S NAME: Copley Pharmaceutical, Inc.			
APPLICANT'S ADDRESS: 25 John Road Canton Commerce Center Canton, MA 02021-2897			
COMMENTS : Top 200			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY~	
1. Applicant	Manufacturing and testing facility	liq	COJC 21684	AC	1/26/96
(b)(4)(CC) [redacted]					9/12/94
					1/12/95
					10/8/93
Acton, MA 01720				AC	4/30/96

FOR HFD-324 USE ONLY:	CSO Thurmette Ferguson	DATE RECEIVED	5/1/96
	CGMP COMPLIANCE STATUS Acceptable	DATE	5/8/96

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.
cc: ANDA 74-873 HFD-629/Div File, HFD-617/JWilson, HFD-617/TAmes, HFD-629/JSimmons HFD-629/GJSmith
File\eerforms\74873

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74873

CORRESPONDENCE

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

March 27, 1996

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
Room 150
Rockville, MD 20855-2773

RE: ANDA Submission
Tretinoin Solution; Topical, 0.05%

Dear Mr. Sporn:

Copley Pharmaceutical, Inc. (Copley) respectfully submits for your Division's review and approval our Abbreviated New Drug Application (ANDA) for Tretinoin Solution; Topical, 0.05% that is bioequivalent to the listed drug, Retin-A® Liquid, 0.05% manufactured by Dermatological Division Ortho Pharmaceutical Corporation pursuant to NDA #16-921.

This application is submitted in accordance with the guidelines set forth in Section 505(j) of the Federal Food, Drug, and Cosmetic Act and consists of one volume. Copley is filing an archival copy (in a blue folder) of the ANDA that contains all the information required in the ANDA and a technical review copy (in a red folder) which contains all the information in the archival copy.

Copley is requesting a waiver, as provided for in 21 CFR § 320.22, from the performance of in-vivo bioequivalence studies since the product is a solution intended for topical administration.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are (617) 575-7520 (direct dial) and (617) 575-7362 (fax).

This also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to the New England District Office. This "field copy" was contained in a burgundy folder.

Thank you for your prompt handling of this submission.

Sincerely,

William E. Brochu, Ph.D.
Director, Regulatory Affairs

Enclosures:

Archive Copy (blue folder)
Manufacturing Section (red folder)
Analytical Section (2 copies, separate binders)