

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-600

CORRESPONDENCE

1077

NDA 20-600

JUN 28 1996

Allergan, Inc.
Attention: Trudy A. Rumbaugh, M.D.
Director, Global Regulatory Affairs, Retinoids
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92713-9534

Dear Dr. Rumbaugh:

Please refer to your June 16, 1995, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tazarotene gel, 0.05% and 0.1%.

As previously communicated in our Not Approvable letter of June 6, 1996, the proposed proprietary name for this drug product, "ZoracTM" was judged to be unacceptable by the CDER Labeling and Nomenclature Committee.

Specifically, the CDER Labeling and Nomenclature Committee identified existing proprietary names that may conflict with the proposed name, "ZoracTM." Such potential look alike/sound alike proprietary names include: XERACTM, ZIACTM, SERAXTM, ZOVIRAXTM, and ZANTACTM. Although, SERAXTM, ZIACTM and ZANTACTM are all oral solids and present little potential for conflict, XERACTM and ZOVIRAXTM are both topical products and have a high potential for confusion.

Should you have any questions regarding this application, please contact:

Frank Cross, Jr., MA, LCDR
Project Manager
(301) 827-2020

Sincerely yours,



Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

NDA 20-600

Page 2

cc:

Orig NDA 20-600

HFD-540

HFD-105/Weintraub

HFD-540/Division File

HFD-2/Lumpkin

HFD-735

HFA-100

HFC-130

HFD-82

HFD-800

District Office

HF-2/Medwatch

HFD-40/Raymond

HFD-613

HFD-638

HFD-530/Boring

HFD-540/Derm File

HFD-540/MO/Ko

HFD-540/CHEM SUPV/DeCamp

HFD-540/PHARM SUPV/Jacobs

HFD-160/SUPV MICRO/Cooney

HFD-880/BIOPHARM SUPV/Bashaw

HFD-725/BIOSTAT SUPV/Srinivasan

HFD-160/CHEM/Gilman

HFD-160/MICRO/Hughes

HFD-540/PHARM/Nostrandt

HFD-725/BIOSTAT/Thomson

HFD-880/BIOPHARM/Lee

HFD-540/PROJ MGR/Cross/rev1-6.19.96/rev2-6.19.96rev3-6.24.96

Concurrence:

HFD-540/DIV DIR/Wilkin/6.21.96

HFD-540/DEP DIR/Katz/6.21.96

HFD-830/DIV DIR/Sheinin/6.24.96

HFD-540/PROJ MGT SUPV/Cook/6.19.96

GENERAL CORRESPONDENCE

Memorandum

MAY 23 1996

To: Mr. Frank Cross

Re: Requested information for statistical carcinogenicity analysis.

NDA/ Drug Class: 20-600 / 1S

Name of Drug: Tazarotene Gel, 0.05%, 0.1% (Zorac™)

Applicant: Allergan, Inc.

From my vast experience with carcinogenicity studies we will always do at least three analyses: 1) dietary/weight gain, 2) general survival, and 3) tumorigenicity. For the 1st analysis I need some indication of each animal's treatment group and their weight (say gms) and food consumption (say gms/day or gms/kg/day) at various times during the study. For the second analysis a time to death or loss to the study (e.g. sacrifice), along with treatment is needed. For the third analysis, if any was performed, I need the results of microscopic histopathologic evaluation of each organ of interest, a summary of all tumors found, and an assessment of whether or not the tumor killed the animal. For skin tumors, probably the primary interest here, we need a record of when the tumor became manifest, whether it killed the animal, etc.

What I have now is a series of numbers that purport to describe the tumorigenicity, but without a code book, seem to be just sequences of numbers. There are some sequences that look like they might be onset dates or times of death, but they have some consistency problems. Hopefully, this is just a reflection of the fact that I am missing something in the data, but it does cause me some concern. This would be cleared up if I had a code book for the data. Other items might be needed depending on the wishes of the toxicologist.

So what I need is:

- 1) dietary data set with weight gain and food consumption.
- 2) a code book for the tumorigenicity data.

If the tumorigenicity data does not include survival or onset information, I need that as well:

- 3) survival and onset data for tumors.

Muchos gracias.

Steve Thomson 05-23-96
Steve Thomson
Mathematical Statistician, Biometrics IV

R. Srinivasan 05/23/96

concur: R. Srinivasan, Ph.D.
Acting Team Leader, Biometrics IV

cc:
~~HFD540/Mr. Cross~~
HFD-725/Mr. Thomson
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
This memo has 1 page
\\Thomson\WP Text\7-2078\May 21, 1996\c:\wpfiles\memo1.wp

MEMORANDUM

MAY 22 1997

TO: Dennis Bashaw, Pharm.D., Team Leader, DPE III *ELU 5/22/97*

FROM: Sue-Chih Lee, Ph.D., Pharmacokinetic Reviewer, DPE III *SEL 5/22/97*

DATE: May 22, 1997

SUBJECT: NDA 20-600/Tazarotene Gel, 0.05% and 0.1%
Phase IV Request - Drug-Drug Interaction Studies

Because of the potential teratogenic toxicity of tazarotene after topical applications, there are concerns regarding the efficacy of oral contraceptives when patients are treated with topical tazarotene. For this reason, it is considered necessary that the sponsor commit to conduct Phase IV drug-drug interaction studies. The following points should be considered:

1. The study should include patients with large surface area of psoriatic skin. The study design for topical administration of tazarotene should be similar to that in study R168-153-8606 and the plasma concentration-time profile for tazarotene should be determined.
2. Both combination and single-entity oral contraceptives should be studied.

CC:
NDA 20-600
HFD-540 (Div. File)
HFD-540 (CSO/Cintron)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

RECORD OF TELECON

DATE: August 21, 1996

PARTICIPANTS FROM THE FDA:

F. Cross, Project Manager

PARTICIPANTS FROM THE SPONSOR

Tom Walton, Regulatory Affairs, Allergan

SUBJECT: NDA 20-600, tazarotene gel, 0.05%, 0.1%

OBJECTIVE: Telecon to Discuss Proposed Name - Zorac

I had the following conversation with Mr. Walton:

Per the recommendation of the team, the proposed name Zorac will not be approved in the Action letter that will be sent to the Applicant of this NDA due to the following reasons:

- As previously communicated in our Not Approvable letter of June 6, 1996, the proposed proprietary name for this drug product, "ZoracTM" was judged to be unacceptable by the CDER Labeling and Nomenclature Committee. Specifically, the CDER Labeling and Nomenclature Committee identified existing proprietary names that may conflict with the proposed name, "ZoracTM." Such potential look alike/sound alike proprietary names include: XERACTM, ZIACTM, SERAXTM, ZOVIRAXTM, and ZANTACTM. Although, SERAXTM, ZIACTM and ZANTACTM are all oral solids and present little potential for conflict, XERACTM and ZOVIRAXTM are both topical products and have a high potential for confusion.
- Not in accordance with 21 CFR 201.10 (c) (5)

The telecon ended amicably.



Frank H. Cross, Jr., MA, LCDR
Project Manager, HFD-540

cc:

Orig. NDA 20-600

HFD-540

HFD-540/DIV DIR/Wilkin

HFD-540/DEP DIR/Katz

HFD-830/Sheinin

HFD-540/MO/Ko

HFD-540/SCHEM/DeCamp

HFD-160/CHEM/Gilman

HFD-540/SRTOX/Jacobs

HFD-540/PHARM/Nostrandt

HFD-725/SBIOSTAT/Srinivasan

HFD-725/BIOSTAT/Thomson

HFD-160/MICRO/Hughes

HFD-880/SBIOPHARM/Bashaw

HFD-880/BIOPHARM/Lee

HFD-540/SPM/Kozma-Fornaro

~~HFD-540/PM/Cross~~

MEMORANDUM OF TELECON

11.0.96
Cross

NDA 20-600
Telecon
Page 1

Telecon Date: October 9, 1996 Time: 1515 Location: N229

NDA 20-600, tazarotene gel, 0.05%, 0.1%

Sponsor: Allergan, Inc.

Meeting Chair: Frank Cross, Jr., MA, LCDR

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., MA, LCDR

FDA Attendees, titles and offices:

Frank Cross, MA, LCDR, Regulatory Management Officer, DDDDP, HFD-540
Sue Chih-Lee, Ph.D., Biopharmaceutist, HFD-880

Sponsor Attendees, titles and offices:

Tom Walton, Allergan
Diane Tong-Liu, Allergan
Richard Matsumoto, Allergan

Meeting Objectives:

Discussion of room temperature stability of tazarotene gel.

Decisions (agreements) reached:

The data received by FAX is closer to what we need. We will have an internal discussion and get back to the applicant on 10/10/96.

Unresolved issues or issues requiring further discussion:

None.

Signature, minutes preparer: 
Concurrence Chair (or designated signatory): 

NDA 20-600

Telecon

Page 2

cc:

Orig NDA 20-600

HFD-540

HFD-540/DIV DIR/Wilkin

HFD-540/DEP DIR/Katz

HFD-540/MO/Ko

HFD-540/SR TOX/Jacobs

HFD-540/SCHEM/DeCamp

HFD-725/SBIOSTAT/Srinivasan

HFD-725/BIOSTAT/Thomson

HFD-880/SBIOPHARM/Lee/10.10.96

HFD-540/PHARM/TOX/Nostrandt

HFD-720/DIV DIR/Sheinin

HFD-540/PM/Cross/rev1-10.9.96

TELECON MINUTES

Telecon Date: October 31, 1996

Time: 1400

Location: N229

NDA 20-600, tazarotene gel, 0.05%, 0.1%

Sponsor: Allergan, Inc.

NDA Meeting to resolve questions regarding the MV package issues from FAX dated 10/25/96

Meeting Chair: Wilson DeCamp, Ph.D., Chemistry Team Leader

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., MA, LCDR

FDA Attendees, titles and offices:

Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540

Sydney Gilman, Ph.D., Chemist Reviewer, HFD-160

Frank Cross, MA, LCDR, Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Tom Walton, Manager, Regulatory Affairs, Allergan

Trudy Rumbaugh, Director, Global Regulatory Affairs, Retinoids, Allergan

John Kent, V.P., Chemical Sciences, Allergan

Lloyd Takahashi, Director, Pharmaceuticals Analysis

Rick Bunnell, Director, Preformulations Group

Meeting Objectives:

To answer concerns/questions raised from the FAX issues re: the Methods Validation Package previously FAXED to the applicant.

Discussion Points (see attached):

Decisions (agreements) reached:

Drug Substance:

1. The Agency will relook at the rebuttal statement in the Faxed response and the March submission in MV package submitted. The applicant said they had submitted the independent accuracy determinations of tazarotene and its impurities so as to show accuracy of the method.
2. The Agency accepts the explanation (attached).

3. The applicant restated #1 and referenced page 60 of the MV package.

Drug Product:

1. Should be drug substance. Some of the parameters changed. The Agency said it will check for documentation in the package and will get back to the applicant if this documentation is not located. Short description on page 16 of MV package.
2. The applicant will submit a 68% level for our review.
3. The applicant will re-examine the BHA and BHT assays for accuracy and linearity and will submit this to the Agency.

Unresolved issues or issues requiring further discussion:

None

Signature, minutes preparer:

Concurrence Chair (or designated signatory):

J. B. [Signature] MA, LSP
William H. DeCamp, Ph.D.

Attachment

NDA 20-600

Page 3

cc:

Orig NDA 20-600

HFD-540

HFD-540/DIV DIR/Wilkin

HFD-540/DEP DIR/Katz

HFD-540/MO/Ko

HFD-540/SRTOX/Jacobs

HFD-540/SCHEM/DeCamp

HFD-160/CHEM/Gilman

HFD-725/SBIOSTAT/Srinivasan

HFD-725.BIOSTAT/Thomson

HFD-880/SBIOPHARM/Bashaw

HFD-880/BPHARM/Lee

HFD-540/PHARM/Nostrandt

HFD-540/PM/Cross/rev1-10.31.96

TELECON MINUTES

NDA 20-600

Page 1.

Telecon Date: January 9, 1997

Time: 1400

Location: N229

NDA 20-600. tazarotene gel, 0.05%, 0.1%

Sponsor: Allergan, Inc.

NDA Meeting to resolve questions regarding the MV package issues from FAX dated 10/25/96

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., MA, LCDR

FDA Attendees, titles and offices:

Hon Sum Ko, M.D., Medical Officer, DDDDP, HFD-540

Steve Thomson, Ph.D., Biostatistician, DOBIV, HFD-725

Kevin Darryl White, Project Manager, DDDDP, HFD-540

Frank Cross, MA, LCDR, Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Tom Walton, Manager, Regulatory Affairs, Allergan

Trudy Rumbaugh, Director, Global Regulatory Affairs, Retinoids, Allergan

John Lue, Biostatician, Allergan

Meeting Objectives:

To discuss the safety update request asked for in the AE letter of 12/30/96

Discussion Points:

Decisions (agreements) reached:

With reference to the safety update portion of the Approvable Letter dated December 30, 1996, the Agency advised the Applicant to submit all of the Adverse Event data individually. After the data is reviewed, the Agency advised the Applicant that the data may need to be pooled depending on how the data looks. The Applicant agreed.

The Applicant asked for clarification with regard to the first sentence of question 6 in the Approvable Letter dated December 30, 1996, i.e., "Information on follow-up of the three babies born of mothers who became pregnant while being treated with tazarotene in the clinical trials is needed." The Agency restated the request.

The Applicant mentioned that the information may be somewhat difficult to obtain. However, the Applicant agreed to submit whatever information is available.

NDA 20-600

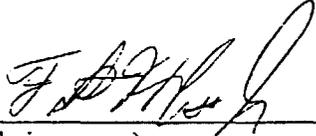
Page 2

The Applicant stated that they anticipate submitting the response to the Approvable Letter on January 17, 1997.

Unresolved issues or issues requiring further discussion:

None

Signature, minutes preparer:



Concurrence Chair (or designated signatory): _____

cc:

Orig NDA 20-600

HFD-540

HFD-540/DIV DIR/Wilkin

HFD-540/MO/Ko

HFD-540/SRTOX/Jacobs

HFD-540/SCHEM/DeCamp

HFD-160/CHEM/Gilman

HFD-725/SBIOSTAT/Srinivasan

HFD-725/BIOSTAT/Thomson

HFD-880/SBIOPHARM/Bashaw

HFD-880/BPHARM/Lee

HFD-540/PHARM/Nostrandt

HFD-540/PM/Cross/rev1-1.9.96

TELECON MINUTES

Telecon Date: April 2, 1997

Time: 1415

Location: N229

NDA 20-600, Tazorac (tazarotene gel) Gel, 0.05%, 0.1%

Sponsor: Allergan, Inc.

Meeting Chair: Frank H. Cross, Jr., M.A., LCDR

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., LCDR

FDA Attendees, titles and offices:

Frank Cross, M.A., LCDR, Regulatory Management Officer, DDDDP, HFD-540

Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540

Sydney Gilman, Ph.D., Chemist Reviewer, HFD-160

Sponsor Attendees, titles and offices:

Trudy A. Rumbaugh, M.D., Director, Global Regulatory Affairs, Retinoids, Allergan

Richard Bunell, Manager of Pre-Formulation

Elizabeth Syage, Director, R&D, Process Chemistry

James Currie, Manager, Worldwide Operations

Meeting Objectives:

To transmit issues pertinent to the scale-up procedures for the Bulk Drug Substance at the facility.

Decisions (agreements) reached:

The Applicant agreed to submit the following:

1. Procedural details for the manufacture of 35 to 60kg of the bulk drug substance at the facility.
2. A comparison of the new drug substance under controlled room temperature and accelerated storage release and at three months to date from a previous lot, 120 days post approval.
3. Since this drug substance will be used in the manufacture of Tazorac prior to the Agency's request for lot comparisons, a commitment to remove from the commercial manufacture any lot failing to meet acceptance criteria.

NDA 20-600

Page 2

Unresolved issues or issues requiring further discussion:

None.

Signature, minutes preparer:



cc:

Orig NDA 20-600

HFD-540

HFD-540/DIV DIR/Wilkin

HFD-540/MO/Ko

HFD-540/PHARM TOX TL/Jacobs

HFD-540/PHARM TOX/Nostrandt

HFD-540/CHEM TL/DeCamp

HFD-160/CHEM/Gilman

HFD-725/BIOSTAT TL/Srinivasan

HFD-725/BIOSTAT/Thomson

HFD-880/BIOPHARM TL/Bashaw

HFD-880/BIOPHARM/Lee

HFD-540/SPM/Kozma-Fornaro

HFD-540/PM/Cross/rev1-4.8.97

MEMORANDUM OF TELECON

ORIGINAL

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500



December 4, 1996

BC

NDA ORIG AMENDMENT

Jonathan Wilkin, MD
Acting Director,
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



REF: NDA 20-600/Tazorac™ (tazarotene) 0.05%, 0.1% Gel
Labeling for Container/Closure Systems--New Drug Product

Dear Doctor Wilkin:

Allergan hereby submits, to the above-referenced NDA, a review and archival copy of our proposed labeling for the container/closure system and cartons for the new drug product. Previously we have faxed and supplied by courier identical copies of this material to the Project Manager, Frank Cross, Jr.

We ask that the enclosed container and carton labeling copy be reviewed and retained in the file of NDA 20-600, Tazorac™ Gel. If you should have any other questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE
OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314)

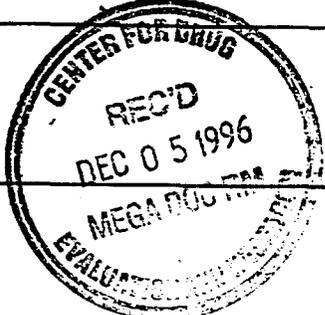
Form Approved: OMB No. 0910-0001
 Expiration Date: December 31, 1992
 See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT Allergan, Inc.	DATE OF SUBMISSION 12/4/96
ADDRESS (Number, Street, City, State and Zip Code) 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534	TELEPHONE NO. (Include Area Code) (714) 752-4500
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) NDA 20-600

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN) Tazarotene	PROPRIETARY NAME (if any) Tazorac Gel	
CODE NAME (if any) AGN 190168	CHEMICAL NAME	
DOSAGE FORM Topical Gel	ROUTE OF ADMINISTRATION Topical	

PROPOSED INDICATIONS FOR USE

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
--------------	--------------------------------

TYPE SUBMISSION (Check one)

PRESUBMISSION AN AMENDMENT TO A PENDING APPLICATION SUPPLEMENTAL APPLICATION
 ORIGINAL APPLICATION RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS (Check one)

APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION

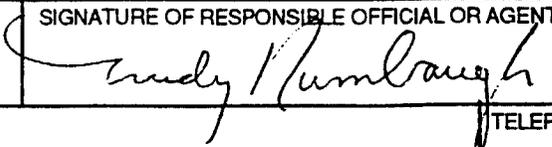
This application contains the following items: *(Check all that apply)*

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Summary (21 CFR 314.50(c))
<input type="checkbox"/>	3. Chemistry, manufacturing, and control section (21 CFR 314.50(d)(1))
<input type="checkbox"/>	4. a. Samples (21 CFR 314.50(e)(1)) (Submit only upon FDA's request)
<input type="checkbox"/>	b. Methods Validation Package (21 CFR 314.50(e)(2)(i))
<input checked="" type="checkbox"/>	c. Labeling (21 CFR 314.50(e)(2)(ii))
	i. draft labeling (4 copies)
	ii. final printed labeling (12 copies)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50(d)(2))
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50(d)(3))
<input type="checkbox"/>	7. Microbiology section (21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (21 CFR 314.50(d)(5))
<input type="checkbox"/>	9. Safety update report (21 CFR 314.50(d)(5)(vi)(b))
<input type="checkbox"/>	10. Statistical section (21 CFR 314.50(d)(6))
<input type="checkbox"/>	11. Case report tabulations (21 CFR 314.50(f)(1))
<input type="checkbox"/>	12. Case reports forms (21 CFR 314.50(f)(1))
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
<input checked="" type="checkbox"/>	15. OTHER (<i>Specify</i>) Container/Closure System and Carton Labeling

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

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

NAME OF RESPONSIBLE OFFICIAL OR AGENT Trudy A. Rumbaugh, M.D., Director Global Regulatory Affairs, Retinoids	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	DATE = 12/4/96
ADDRESS (Street, City, State, Zip Code) 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534		TELEPHONE NO. (Include Area Code) (714) 246-4292

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)



2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

December 5, 1996

BL
NDA ORIG AMENDMENT

Jonathan Wilkin, MD
Acting Director,
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
2301 Corporate Blvd., Building 2
Rockville, MD 20850

REF: NDA 20-600/Tazorac™ (tazarotene) 0.05%, 0.1% Gel
Official Submission of Proposed Labeling faxed on November 25, 1996

Dear Doctor Wilkin:

Allergan hereby submits, to the above-referenced NDA, a review and archival copy of the proposed Draft Labeling faxed to you on the evening of November 25, 1996. This official submission is in response to a request by the Project Manager, Frank Cross, Jr.

We ask that the enclosed labeling be reviewed and retained in the file of NDA 20-600, Tazorac™ Gel. If you should have any other questions or require additional information, please contact me at 714.246.4470 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids



TR/tww

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 PUBLIC HEALTH SERVICE
 FOOD AND DRUG ADMINISTRATION
**APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE
 OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-001
 Expiration Date: November 30, 1995
 See OMB Statement on Page 3

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT Allergan, Inc.	DATE OF SUBMISSION 6-28-95
ADDRESS (Number, Street, City, State and Zip Code) P.O. Box 19534 2525 Dupont Drive Irvine, CA 92713-9534 USA	TELEPHONE NO. (Include Area Code) 1-800-347-4500
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (if previously issued) NDA 20-600

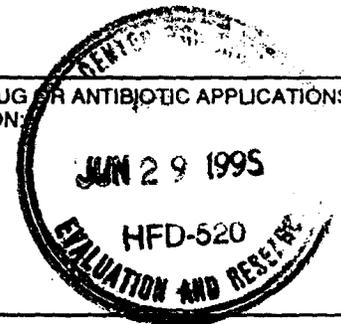
DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN) USAN: Tazarotene	PROPRIETARY NAME (if any) None
CODE NAME (if any) AGN 190168	CHEMICAL NAME Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate
DOSAGE FORM Topical Gel	ROUTE OF ADMINISTRATION Topical
	STRENGTH(S) 0.05% 0.1%

PROPOSED INDICATIONS FOR USE
 Once daily treatment of plaque psoriasis
 Once daily treatment of acne vulgaris

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

IND
 DMF
 DMF
 DMF
 DMF



INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
--------------	--------------------------------

TYPE OF SUBMISSION (Check one)

PRESUBMISSION AN AMENDMENT TO A PENDING APPLICATION SUPPLEMENTAL APPLICATION
 ORIGINAL APPLICATION RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70 (b) (2) (iv)) _____

PROPOSED MARKETING STATUS (Check one)

APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION

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

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
<input type="checkbox"/>	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
<input type="checkbox"/>	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
<input checked="" type="checkbox"/>	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling (4 copies)
	ii. final printed labeling (12 copies)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
<input type="checkbox"/>	7. Microbiology section (21 CFR 314.50 (d) (4))
<input type="checkbox"/>	8. Clinical data section (21 CFR 314.50 (d) (5))
<input type="checkbox"/>	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
<input type="checkbox"/>	10. Statistical section (21 CFR 314.50 (d) (6))
<input type="checkbox"/>	11. Case report tabulations (21 CFR 314.50 (f) (1))
<input type="checkbox"/>	12. Case report forms (21 CFR 314.50 (f) (1))
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
<input checked="" type="checkbox"/>	15. OTHER (Specify) Revised Annotated Labeling

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contra-indications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

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

NAME OF RESPONSIBLE OFFICIAL OR AGENT Trudy A. Rumbaugh, M.D., Director Global Regulatory Affairs, Retinoids	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Trudy Rumbaugh M.D.</i>	DATE 6/28/95
--	--	-----------------

ADDRESS (Street, City, State, Zip Code) 2525 Dupont Drive, P.O. Box 19534 Irvine, CA 92713-9534	TELEPHONE NO. (Include Area Code) (714) 246-4292-
--	--

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500



June 10, 1997

Jonathan Wilkin, MD
Acting Director
Division of Dermatological and Dental Drug Products
HFD-540/Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, Building 2
Rockville, MD 20850

**REF: NDA 20-600/Tazorac™ (tazarotene topical gel) 0.05%, 0.1% Gels
Response to receipt of revised Draft Labeling; June 10, 1997**

Dear Doctor Wilkin:

Allergan is notifying you, by this letter, of our formal acceptance of the revised Draft Labeling received by facsimile today for the above-referenced NDA.

This letter will be formally submitted to the NDA by overnight courier. If you should have any questions or require additional information, please contact Trudy Rumbaugh at 714.246.4292 or Thomas Walton at 714.246.4470.

Sincerely,

Peter A. Kresel, MS, MBA
Vice President,
Global Regulatory Affairs

PK/tww

ALLERGAN



2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

June 11, 1997

Jonathan Wilkin, MD
Acting Director
Division of Dermatological and Dental Drug Products
HFD-540/Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, Building 2
Rockville, MD 20850

**REF: NDA 20-600/Tazorac™ (tazarotene topical gel) 0.05%, 0.1% Gels
Response to Request for Phase 4 Commitments; June 11, 1997**

Dear Doctor Wilkin:

Allergan is notifying you, by this letter, of our formal statement of commitment for the Phase 4 commitments requested by FDA and received by facsimile today for the above-referenced NDA.

This letter will be formally submitted to the NDA by overnight courier. If you should have any questions or require additional information, please contact Trudy Rumbaugh at 714.246.4292 or Thomas Walton at 714.246.4470.

Sincerely,

Peter A. Kresel, MS, MBA
Vice President,
Global Regulatory Affairs

PK/tww

June 28, 1995

Jonathan Wilkin, MD
Director,
Division of Topical Drug Products
Center for Drug Evaluation and Research
HFD-540/Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



REF: NDA 20-600, Tradename™ (tazarotene) 0.05%, 0.1% Gel
Submission of Requested Data: Microbiology/Preservative Efficacy

Dear Doctor Wilkin:

Allergan, Inc., hereby amends, the above-referenced NDA with portions of the Chemistry, Manufacturing and Controls section concerning Preservative Effectiveness and information on the preservative (Benzyl Alcohol NF) of the finished dosage form, Tazarotene Gel. This information has been requested by Joanne Holmes, Project Manager.

Since the new drug substance, Tazarotene, is a synthetic retinoid and is not derived from either animal or plant tissues and since it is produced in reactors in which the final steps involve rinsing and recrystallization with organic solvents, microbial contamination is not a concern. This has been shown by laboratory data generated in our Research Department.

This amendment contains the following:

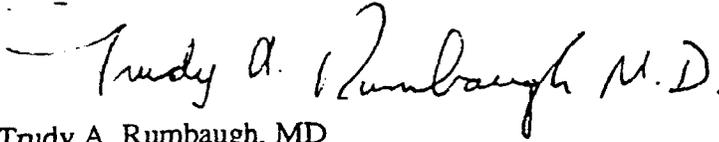
- Table of all components and compendial grades of the new drug product
- Table of all component tests and specifications
- Tables of the quantitative composition of each formulation (0.05%, 0.1%)
- Tables of the in-process and release specifications
- New drug product specifications and the rationale for the specifications
- Rationale for the analytical procedures chosen
- The HPLC analytical procedure for Benzyl Alcohol NF (the preservative)
- Portions of the stability report that focus on Preservative Efficacy and Benzyl Alcohol concentration

This submission's data previously submitted in the NDA. The original pagination has been retained so that reviewers can more easily determine the original location of the information (volume followed by page number in lower right corner of each page).

NDA 20-600
06/28/95
Pg. 2 of 2

Please let us know if you have any further questions or require additional information. I can be reached at 714.246.4292 or contact Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

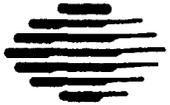


Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 • (714) 752-4500



~~CONFIDENTIAL~~
NC

DUPLICATE

July 10, 1995

Jonathan Wilkin, MD
Director,
Division of Topical Drug Products
Center for Drug Evaluation and Research
HFD-540/Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REF: NDA 20-600, Tradename™ (tazarotene) 0.05%, 0.1% Gel
Pre-Approval Inspection Certification

Dear Doctor Wilkin:

Allergan, Inc., hereby certifies that we are prepared for a Pre-Approval Inspection of our research and manufacturing facilities upon FDA's acceptance of the above-referenced NDA for filing.

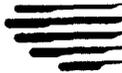
We request, however, that FDA's Dallas and Los Angeles District Offices contact us so that we can arrange for a mutually acceptable date and so that we may make arrangements for the appropriate representatives of both the Agency and Allergan to be present at the respective facilities.

Please let me know if you have further questions or require additional information. We ask that this information be reviewed and retained in the file of NDA 20-600, Tazarotene Gel.

Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww



July 26, 1995

Jonathan Wilkin, MD
Director,
Division of Topical Drug Products
Center for Drug Evaluation and Research
HFD-540/Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REF: NDA 20-600, Tradename™ (tazarotene) 0.05%, 0.1% Gel
Chemistry, Manufacturing and Controls Amendment

Dear Doctor Wilkin:

Allergan, Inc., hereby amends, the Chemistry, Manufacturing and Controls section of the above-referenced NDA that concerns the analytical procedure for the New Drug Products, Tazarotene 0.05% and 0.1% Gels. Specifically, during our QA Audit, we discovered some minor inconsistencies in the references in the analytical procedures for each dosage form contained in the NDA and the analytical procedures that are currently being used in the validation in our Waco, Texas manufacturing facility. This amendment will bring the NDA into alignment with the analytical procedures that are being used in Waco, Texas.

Therefore we are amending the analytical procedure for each dosage form (0.05% and 0.1% gels) as presented in the table on the following page.

Please note that only one of the revisions, a change in sample preparation for the assay for benzyl alcohol, affects the performance of the assay and represents a change from that submitted in the NDA with that being performed in our manufacturing facility. This sample preparation change has been validated.

Please let us know if you have any further questions or require additional information. I will be on medical leave until August 7; in the meantime, please contact Thomas Walton at 714.246.4470, Pacific Time.

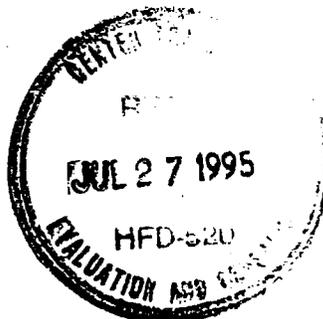
We ask that this material be reviewed and retained in the file of NDA 20-600, Tazarotene Gel.

Sincerely,

Thomas Walton / for

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww



DUPLICATE

ALLERGAN

2525 Dupont Drive, PO. Box 19534, Irvine, CA 92713-9534 • (714) 752-4500



September 21, 1995

Jonathan Wilkin, MD
Director,
Division of Topical Drug Products
Center for Drug Evaluation and Research
HFD-540/Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESPONDENCE

REF: NDA 20-600, Tradename™ (tazarotene) 0.05%, 0.1% Gel
Request for Telephone Conference--Chemistry, Manufacturing and Controls

Dear Doctor Wilkin:

Allergan, Inc., hereby requests, a Telephone Conference Call Meeting with Wilson DeCamp, Ph.D., Supervisory Chemist. Specifically, we seek Dr. DeCamp's Chemistry expertise and regulatory advise concerning the scale-up of our New Drug Substance.

Although we are aware of Office of Generic Drug Products' Guidelines for Bulk Drug Substances and other FDA Guidelines for New Drug Products, we are unaware of specific guidelines concerning the scale-up of New Chemical Entities. We are moving to our scale-up activities in the very near future and therefore require guidance from the Division.

The tentative list of Allergan attendees at the telephone conference are:

John Kent, Ph.D., Vice President, Pharmaceutical Sciences
Elizabeth Syage, Ph. D., Manager, Chemical Sciences
Thomas Walton, Specialist, Regulatory Affairs

It is possible there may be several additional Pharmaceutical Sciences or Regulatory Affairs attendees. Our sole agenda item is the Bulk Drug Substance scale-up.

We realize the demands on the Division for meetings and telephone conferences are many. We plan to keep this meeting as brief as possible. If Dr. DeCamp could give us several possible times he is available for the meeting, we will be able to work with Ms. Sandy Childs in order to set up a mutually agreeable time. Please keep in mind the 3-hour time difference between our locations. I can be reached at 714.246.4292 or Thomas Walton at 714.246.4470.

Sincerely,

Thomas Walton / for

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww





September 22, 1995

Jonathan Wilkin, MD
Director,
Division of Topical Drug Products
Center for Drug Evaluation and Research
HFD-540/Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

BC
RECEIVED

REF: NDA 20-600, Tradename™ (tazarotene) 0.05%, 0.1% Gel
Chemistry, Manufacturing and Controls Amendment

Dear Doctor Wilkin:

Allergan, Inc., hereby amends, the Chemistry, Manufacturing and Controls section of the above-referenced NDA. Specifically, we are correcting and clarifying several minor issues concerning the New Drug Product, Tazarotene Gel. The corrections/clarifications are as follows:

- The Release Specifications (Vol. 3, Pg. 182) list the Preservative Efficacy Test (PET) as the microbiology test performed at product release. The correct test is the Microbial Limits Test (MLT). PET is performed at the end of the proposed shelf life.
- The Standard Operating Procedure (SOP) for the receipt of incoming components for Tazarotene Gel is listed as SOP HQC-002 (Volume 8, Page 127, Appendix 3.7.5A). This is the SOP in place for our Irvine, California, facility. The analogous SOP for our Waco, Texas, manufacturing facility is SOP WQA-004 (Volume 8, Page 001, Appendix 3.7.4A).
- The Stability Protocols (Volume 10, Pages 176-179, Master #10WW) were the stability protocols utilized for the Manufacturing Site Validation Lots and included protocols for accelerated testing. These protocols are labeled "Not for Manufacturing Use." The Stability Protocols to be utilized for regular production lots have been re-issued (Volume 9, Pages 1-2, Master #11WW).

If you have further questions or require additional information, please contact either myself at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

We ask that this material be reviewed and retained in the file of NDA 20-600, Tazarotene Gel.

Sincerely,

Thomas Walton

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww





Orif
NC

October 17, 1995

Jonathan Wilkin, MD
Director,
Division of Topical Drug Products
Center for Drug Evaluation and Research
HFD-540/Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REF: NDA 20-600, Tradename™ (tazarotene) 0.05%, 0.1% Gel
Combined Psoriasis and Acne Adverse Event Tables

Dear Doctor Wilkin:

Allergan, Inc., hereby amends the above-referenced NDA with Adverse Event (AE) data as requested in a telephone conversation between Thomas Walton of Allergan and Frank Cross, Project Manager, FDA/Topical Drugs.

Mr. Cross requested that Allergan submit a tabular summary of combined AE data from the Phase 3 studies for both indications, acne and psoriasis. Previously, the data was reported separately in the NDA. Therefore, this submission contains AE data in the same format as the original NDA. No new information is included, simply combined AEs. See the Table of Contents section of this amendment for a listing of the tables submitted.

If you have any further questions or require additional information please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

We ask that this information be reviewed and retained in the file of NDA 20-600, Tazarotene Gel.

Sincerely,

Thomas Walton / for

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

cc: Frank Cross, Project Manager (Desk Copy)

TR/tww



12/23/95

ALLERGAN

ORIGINAL
AMENDMENT



25 Dupont Drive, PO. Box 19534, Irvine, CA 92713-9534 · (714) 752-4500

February 5, 1996

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Ophthalmologic Drug Products
Center for Drug Evaluation and Research, HFD-540
Food and Drug Administration
9201 Corporate Blvd, Building 2
Rockville, MD 20857



REF: Zorac™ (tazarotene) 0.05%, 0.1% Gels
NDA 20-600

Dear Doctor Wilkin;

Allergan, Inc. hereby amends, the above-referenced NDA, with information on subjects discontinued from the pivotal clinical trials for administrative (nonmedical) reasons.

This amendment consists of information previously telefaxed to Frank Cross of the Division's Project Management Staff at the request of the Medical Reviewer, Dr. Hon-sum Ko. Dr. Ko wishes to select some of the Case Report Forms to familiarize himself with Allergan's criteria for administrative terminations.

We ask that this information be included in the file of NDA 20-600, Zorac™ Gel. If you have any further questions or require additional information please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

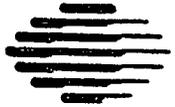
Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

.L.ERGAN

Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 • (714) 752-4500



Electronic Data

February 26, 1996:

Jonathan Wilkin, MD
Acting Director,
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
HFD-540/Room 17B-45
5600 Fishers Lane
Rockville, MD 20857

Bm
NDA ORIG AMENDMENT

REF: Zorac™ (tazarotene) 0.05%, 0.1% Gels
NDA 20-600
Adverse Event and Electronic Data Submission

Dear Doctor Wilkin:

Allergan, Inc., hereby amends, the above-referenced NDA with electronic data and adverse event data as requested by the Medical Reviewer, Doctor Hon-Sum Ko. This material, along with a diskette, has been sent previously and directly to Doctor Ko at the request of the Project Manager, Frank Cross.

This electronic and adverse event data submission consists of the following:

Study R168-145-8606: Electronic Data in ACCESS 2.0
(hard copy of diskette table of contents and diskette data)

Studies R168-120, 121, 125, 126, 145 (psoriasis), 220, 221 (acne)
Adverse event tables tabulated by Body System and Reaction Term
(hard copy)

We ask that this material be retained in the file of NDA 20-600, Zorac™ Gel. If you should have further questions or require additional information please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

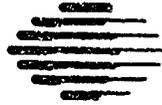
Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww



ALLERGAN

5 Dupont Drive, PO Box 19534, Irvine CA 92713-9534 • (714) 752-4500



February 27, 1996



Jonathan Wilkin, MD
Acting Director,
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products
HFD-540/Room 17B-45
5600 Fishers Lane
Rockville, MD 20857

BC
NDA ORIG AMENDMENT

**REF: NDA 20-600: Zorac™ (tazarotene) 0.05%, 0.1% Gels
Chemistry, Manufacturing and Controls (CMC) Amendment
Drug Product Stability Report, 12-months**

Dear Doctor Wilkin:

Allergan, Inc., hereby amends, the above-referenced NDA with a CMC amendment consisting of a 12-month stability report for the Drug Product, Zorac™ Gel.

Based upon our continued monitoring of the pivotal stability batches, Allergan proposes, at least, an 18-month expiry dating for all tube sizes and for both concentrations for product stored up to 30° C (86° F). We may extend the expiry date, based on further monitoring, consistent with the stability protocol included in this report and also filed with the original application.

A desk copy of this report has been forwarded to Sidney Gilman, Ph.D., in the Division of Medical Imaging and Radiopharmaceutical Drug Products, the acting chemistry reviewer for this NDA.

We ask that this information be reviewed and retained in the file of NDA 20-600, Zorac™ Gel. If you have any further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500

DUPLICATE



NEW CORRESP

NC

March 18, 1996

Jonathan Wilkin, MD
Director,
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
HFD-540/Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REF: NDA 20-600, Zorac™ (tazarotene) 0.05%, 0.1% Gels
Tradename proposal

Dear Dr. Wilkin:

Allergan, Inc. would like to propose the tradename "Zorac" for the 0.05% and 0.1% gel products assigned the USAN (and pINN) generic name "tazarotene". If you could please formally submit this request to the CDER Labeling and Nomenclature Committee it would greatly be appreciated.

Please contact me if you require anything further at 714.246.4292.

Sincerely,

Trudy A. Rumbaugh, M.D.
Director, Global Regulatory Affairs
Retinoids



cc: Frank Cross, Project Manager

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500

ORIGINAL

AMENDMENT

BP



March 19, 1996

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
HFD-540/Room 17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



REF: NDA 20-600/Zorac™ (tazarotene) 0.05%, 0.1% Gels
Study R168-152-8606--Submission of Missing Appendices

Dear Doctor Wilkin:

Allergan, Inc. hereby submits, to the above-referenced NDA, a pharmacokinetic amendment consisting of appendices inadvertently omitted from the final study report. The study, R168-152-8606 entitled "Pharmacokinetics of AGN 190168 0.1% Gel following single-dose and multiple-dose topical administration to healthy subjects," was submitted as part of the original NDA.

We ask that this information be reviewed and amended to NDA 20-600, Zorac™ Gel. If you should have any further questions or require additional information please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

ALLEGAN

525 Dupont Drive, P.O. Box 19554 Irvine, CA 92713-9534 (714) 752-4500

ORIGINAL
AMENDMENT
EM



March 27, 1996

Jonathan Wilkin, MD
Acting Director,
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
HFD-540/Room 17B-45
5600 Fishers Lane
Rockville, MD 20857



REF: Zorac™ (tazarotene) 0.05%, 0.1% Gels
NDA 20-600
Case Report Forms for Study R168-128-8606/Dr. Hon-Sum Ko Request

Dear Doctor Wilkin:

Allergan, Inc. hereby amends the above-referenced NDA with a Review and Archival copy of clinical information requested by the medical reviewer, Hon-Sum Ko, MD.

This amendment consists of Case Report Forms (CRFs) of the patients who were terminated from the study due to adverse events. This information has already been supplied as a Desk Copy to Frank Cross, Project Manager at the Corporate Boulevard office.

We ask that this information be reviewed and retained in the file of NDA 20-600, Zorac™ Gel. Should you have any further questions or require additional information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Rudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

R/tww

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

ALLERGAN

25 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500

**ORIGINAL
AMENDMENT**

EP



April 25, 1996

Mr. Frank Cross, Project Manager
Division of Dermatological and Dental Drug Products
HFD-540/Room N229
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, Building 2
Rockville, MD 20850



**REF: Zorac™ (tazarotene) 0.05%, 0.1% Gels
NDA 20-600
Submission of Toxicology Information**

Dear Mr. Cross:

Referencing our telephone conversation today, Allergan, Inc. is amending the above-referenced NDA with toxicology final study report amendments for the following two carcinogenicity studies:

- Study 1643-ALG/19-943062: AGN 190168 potential tumorigenic effects in prolonged dietary administration to rats
- Study 1643-ALG/25-951336: AGN 190168 potential tumorigenic effects in repeated dermal administration to mice.

These amendments consist of additional histopathological data on 3 female animals in each study. These amendments affected neither the outcome nor the final conclusions of either study.

We ask that this information be reviewed and retained in the file of NDA 20-600, Zorac™ Gel. Should you have any further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500

ORIGINAL

ORIG AMENDMENT



May 21, 1996

BC noted 6/6/96 HSK

Jonathan Wilkin, MD
Acting Director,
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products/ HFD-540
9201 Corporate Blvd., Bldg. 2
Rockville, MD 20850

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> I.L.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

**REF: NDA 20-600: Zorac™ (tazarotene) 0.05%, 0.1% Gels
Chemistry, Manufacturing and Controls (CMC) Amendment
Drug Product Stability Report, 18-months**

Dear Doctor Wilkin:

Allergan, Inc. hereby amends the above-referenced NDA with a CMC amendment consisting of a Review and Archival copy of the 18-month stability report for the Drug Product, Zorac™ Gel.

Based upon our continued monitoring of the pivotal stability batches, Allergan proposes, at least, 24-month expiry dating for all tube sizes and for both concentrations for product stored up to 60° C (86° F). We may extend the expiry date, based on further monitoring, consistent with the stability protocol included in this report and also filed with the original application.

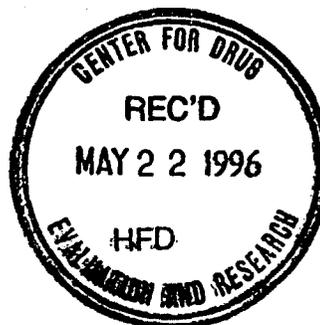
A desk copy of this report has been forwarded to Sidney Gilman, Ph.D., in the Division of Medical Imaging and Radiopharmaceutical Drug Products, the acting chemistry reviewer for this NDA.

We ask that this information be reviewed and retained in the file of NDA 20-600, Zorac™ Gel. If you have any further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww



ALLERGAN

2525 Dupont Drive P O Box 19534 Irvine, CA 92713-9534 (714) 752-4500

DUPLICATE

NEW CORRESP

AC



June 11, 1996

Michael Weintraub, MD
Director, Office of Drug Evaluation V
Center for Drug Evaluation and Research/HFD-105
Central Document Room
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSD ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> MAIL <input type="checkbox"/> MEMO
CSD INITIALS
DATE

REF: NDA 20-600/Zorac™ (tazarotene) 0.05%, 0.1% Gels
Response to Non-Approvable Action Letter of June 6, 1996

Dear Doctor Weintraub:

By this letter Allergan, Inc. is notifying you of our intent to amend the above-referenced NDA. We will respond to all deficiencies noted. As you requested in the Action Letter, we will coordinate our response with the Project Manager assigned to this NDA, Frank Cross, Jr.

If you should have further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

cc: Frank Cross, Jr., Project Manger/DODDDP

TR/tww



(j)(2)(A))

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update reports
es as requested
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Act, I agree

5/96

(ode)

ALLERGAN

10000 Old Drive P.O. Box 19634 Irvine CA 92713-9634 (714) 752-4500



June 27, 1996

Michael Weintraub, MD
Director, Office of Drug Evaluation V
Center for Drug Evaluation and Research/HFD-105
Central Document Room
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

**REF: NDA 20-600/Zorac™ (tazarotene) 0.05%, 0.1% Gels
Response to Non-Approvable Action Letter of June 6, 1996**

Dear Doctor Weintraub:

Allergan, Inc. is amending the above-referenced NDA with responses to the noted deficiencies in the Action Letter of June 6, 1996. This amendment is a complete response to the questions considered the basis of the non-approval action; it addresses all deficiencies listed in the formal Action Letter. In addition, although we will fully respond to the questions considered not the basis of the non-approval action (also dated June 6, 1996), we have included answers to some of these questions at this time. We will fully respond to the remaining questions by July 28, 1996.

This amendment consists of new data, data previously submitted as "desk copies" to the reviewers and clarifications of data from the original NDA, the 120-Day Safety Update and previously submitted amendments.

We ask that this amendment be reviewed and retained in the file of NDA 20-600, Zorac Gel. If you should have further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

cc: Frank Cross, Jr., Project Manger/DODDDP
TR/tww

ALLERGAN

555 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500

June 28, 1996

Frank Cross, Jr., Project Manager
Division of Dermatologic and Dental Drug Products
HFD 540/Room N299
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Noted
FHC

F. J. [unclear]
MA LOR
Project
Manager
7/11/96

REF: NDA 20-600/Zorac™ (tazarotene) 0.05%, 0.1% Gels
Response to Non-Approvable Action Letter of June 6, 1996
Response to "FAX to Allergan" of June 6, 1996

Dear Mr. Cross:

Enclosed are "Desk Copies" of our responses to the above-referenced letter and FAX, both dated June 6, 1996. Since you usually send different sections of submissions to different reviewers we have broken-down our response in this desk copy by scientific discipline. We have combined the "Action Letter" responses with the "FAX to Allergan" responses within the same discipline.

Therefore there are binders for:

<u>Subject</u>	<u>No. of Binders</u>
Chemistry, Manufacturing and Controls	2
Clinical, Safety Update, Safety	2
Biopharmaceutics	1
Microbiology	1
Pharmacology	1
Tradename/Pre-Approval Inspections	1

While we answered all of the questions in the "Action Letter" we have only given a partial response to the questions in the "FAX to Allergan." We anticipate completing our responses to the "FAX to Allergan" by July 28.

NDA 20-600
June 28, 1996

Mr. Cross, Trudy Rumbaugh will be out of the office next week. I will be here Monday and Tuesday; please feel free to call on me for any additional information you may require at 714.246.4470, Pacific Time.

Sincerely,



Thomas W. Walton
Regulatory Affairs Specialist
R&D Regulatory Affairs

DUPLICATE

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500



July 11, 1996

NEW CORRESPONDENCE

-Frank Cross, Jr., Project Manager
Division of Dermatologic and Dental Drug Products
HFD 540/Room N299
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



REF: NDA 20-600/Zorac™ (tazarotene) 0.05%, 0.1% Gels
Response to Non-Approvable Action Letter of June 6, 1996
Response to "FAX to Allergan" of June 6, 1996

Dear Mr. Cross:

This letter is to clarify that the information provided to you as "Desk Copies" of our responses to the above-referenced letter and FAX is identical to the information submitted in the archival copies. The archival copies of the response were sent as an amendment to the NDA on June 27, 1996 and the "Desk Copies" were sent directly to you on June 28, 1996.

Please feel free to call me for any additional information you may require at 714.246.4292, Pacific Time.

Sincerely,

Trudy A. Rumbaugh, M.D.
Director, Global Regulatory Affairs
Retinoids

ALLERGAN

ORIGINAL



10000 Newport Drive, P.O. Box 19534 Irvine, CA 92713-9534 (714) 752-4500

July 22, 1996

NEW CORRESPONDENCE

Eric B. Sheinin, Ph.D.
Director, DNDC III, HFD-830
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



REF: NDA 20-600/Zorac™ (tazarotene) 0.05%, 0.1% Gel
Meeting Confirmation and Background Information

Dear Dr. Sheinin,

This letter is to confirm our meeting that has been scheduled between members of the FDA and Allergan for 27 August 1996 from 8:30-10:30 am in Rockville, Maryland (Corporate Blvd.) concerning the action letter for the above-referenced NDA.

There will be four participants from Allergan in attendance:

Michael E. Garst, Ph.D., MBA, Vice President, Chemical Sciences
John S. Kent, Ph.D., Vice President, Pharmaceutical Sciences
Trudy A. Rumbaugh, MD, Director, Global Regulatory Affairs, Retinoids
Elizabeth T. Syage, Ph.D., Director, Process Chemistry.

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

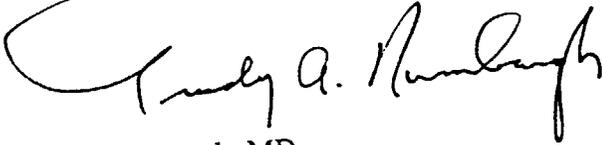
The purpose of this meeting is to better understand the agency's review process and requirements for the chemistry, manufacturing and controls (CMC) section of NDAs with the desire, ultimately, to improve the process. In particular, we would like to review the questions and answers to the nonapproval letter for the Zorac™ (tazarotene) NDA 20-600 (issued on 6 June 1996 and responded to on 27 June 1996). Allergan participated in two constructive teleconferences with Sydney Gilman, chemistry reviewer, on 3 May 1996 and 10 May 1996 at which time the vast majority of the CMC questions were reviewed. We were therefore disappointed when these questions formed the basis for the nonapproval letter. We would like to gain a better understanding of the division's process with the hope that this can be avoided in the future.

Enclosed as background for this meeting is a copy of the not approvable action letter for azarotene NDA 20-600 and the response to the CMC questions in the letter. Please let us know if you would like any of the attachments (the complete response was sent to Dr. Michael Weintraub and a desk copy to Mr. Frank Cross).

Letter to Dr. Sheinin
Page 2 of 2

Should you have any further questions or require additional information, please contact me directly at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,



Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

ALLERGAN

525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500

**ORIGINAL
NEW CORRESP**

NC



July 30, 1996

Michael Weintraub, MD
Director,
Office of Drug Evaluation V/HFD-105
Division Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, Building 2
Rockville, MD 20850



**REF: NDA 20-600/Zorac™ (tazarotene) 0.05%, 0.1% Gels
Response to "FAX to Allergan" dated June 6, 1996**

Dear Doctor Weintraub;

Allergan, Inc. hereby submits, to the above-referenced NDA, a review and archival copy of our response to the "FAX to Allergan" communication received on June 6, 1996. This "FAX..." was received on the same day as the not-approvable Action Letter for the same NDA. Data requested in this "FAX..." were stated to be "...not the basis for the non approvable letter."

This response consists of Chemistry, Biopharmaceutics and Clinical information requested by the Division. Certain observations noted in this "FAX..." were addressed in our formal response to the not approvable Action Letter dated June 27, 1996, and are so noted in this response.

For the convenience of your review, a complete copy of the "FAX to Allergan" communication follows this cover letter. Also for the convenience of your review, we are supplying a "Desk Copy" of this response, under separate cover, to the Project Manager, Frank Cross, Jr. We certify that the "Desk Copy" supplied to Mr. Cross is exactly the same, in form and content, as the review and archival copies enclosed herein.

We ask that this information be reviewed and retained in the file of NDA 20-600, Zorac™ Gel. Should you have any further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Thomas Walton / for

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

cc: Frank Cross, Jr., HFD-540

ALLERGAN



2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

September 4, 1996

Michael Weintraub, MD
Director, Office of Drug Evaluation V
Center for Drug Evaluation and Research/HFD-105
Division Document Room
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



**REF: NDA 20-600/Tradename™ (tazarotene) 0.05%, 0.1% Gels
Response to telephone conversation w/F. Cross concerning tradename**

Dear Doctor Weintraub:

As you are aware, your Division did not approve of our proposed tradename "Zorac" for tazarotene 0.05% and 0.1% gels. This information was reported to us in a telephone call from the FDA project manager, Frank Cross, Jr. In subsequent communications with Mr. Cross concerning tradename issues, we agreed upon a filing strategy wherein we would submit several names in descending order of preference. As the Nomenclature Committee only meets on a monthly basis, this was thought to be the most useful procedure considering that the next user fee action date for NDA 20-600 is January 3, 1997.

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of
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ons,

Therefore, the following four names are being submitted in descending order of preference:

- Tazorac
- Zoac
- ZRC
- Suretin

, I agree

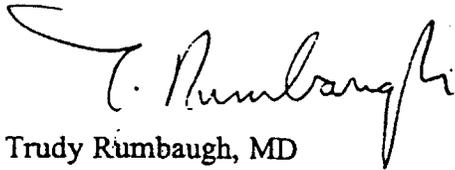
These names have been found by the Patent and Trademark Office to be registerable as trademarks.

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(9)

Rumbaugh to Weintraub
NDA 20-600/Page 2 of 2

We ask that these names be submitted as rapidly as possible to the Nomenclature Committee for their September 1996 meeting. Should you have any questions or require additional information please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,



Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

cc: Frank Cross, Jr. (Fax)

TR/tww

BERKMAN

Mont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500



September 18, 1996

BB

NDA ORIG AMENDMENT

Nathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products/ HFD-540
Center for Drug Evaluation and Research
Food and Drug Administration
201 Corporate Blvd., Building 2
Rockville, MD 20850



SUBJECT: NDA 20-600/Tradename™ (tazarotene) 0.05%, 0.1% Gels
Submission of Pharmacokinetic Report PK-1992-035

Dear Doctor Wilkin,

Allergan, Inc. amends the above-referenced NDA with a pharmacokinetic study consisting of the following report requested by the Project Manager, Frank Cross, Jr.:

Report PK-1992-035: The determination of AGN 190168 and AGN 190299 in human plasma by

We ask that this information in this report be reviewed and filed to NDA 20-600, Tazarotene Gel. If you should have any further questions or require additional information please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Crudy Rumbaugh

Crudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

REVIEWS COMPLETED	
CEO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> V.E.W.O.
_____ INITIALS	_____ DATE

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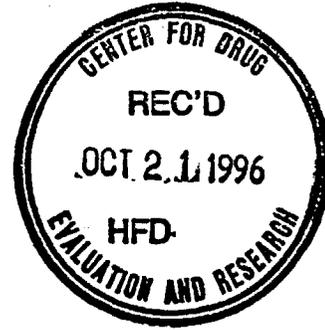
Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500



Statistical Analyses

October 18, 1996

Jonathan K. Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
Food and Drug Administration
Division Document Room/HFD-540
9201 Corporate Boulevard, Building 2
Rockville, MD 20850



REF: Tradename™ (tazarotene) 0.05%, 0.1% Gels
NDA 20-600
Submission of Statistical Analyses Requested by Dr. Hon-Sum Ko
Submission of Revised Environmental Impact Report

Dear Doctor Wilkin:

Allergan amends the above-referenced NDA with a Review and Archival copy of revised statistical analyses as requested by the medical reviewer, Hon-Sum Ko, MD. on October 7. A desk copy of these revised analyses was faxed to the Project Manager, Frank Cross, Jr. on October 17.

Also enclosed is a Review, Archival and Desk Copy of the revised Environmental Impact Statement as requested by the Division.

Ask that this information be reviewed and retained in the file of NDA 20-600, Tazarotene Gel. Should you have any further questions or require additional information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

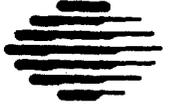
Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

ALLERGAN

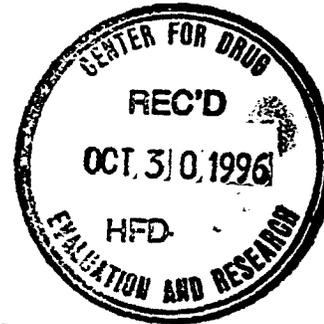
Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

ORIGINAL
NEW CORRESP
VC



October 29, 1996

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research, HFD-540
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard, Building 2
Rockville, MD 20850



**Subject: NDA 20-600
Tazorac™ (tazarotene) 0.05%, 0.1% Gels
Response to Biopharmaceutics Comment and
Submission of Human Blood and Plasma Pharmacokinetic Data**

Dear Doctor Wilkin,

Allergan hereby amends the above referenced NDA with a response to Dr. Lee's clarification of the Action Letter Biopharmaceutics Comment #1-A (page 9) of the 06/06/96 "FAX to Allergan". The clarification (as stated in bold below) was sent by the CDER Project Manager, Frank Cross, via e-mail to Thomas Walton of Allergan and the following identical response was sent to Mr. Cross via fax yesterday, October 28, 1996.

FDA Comment: For the removal of the applied dose at 10 hours after application in Study R168-154-8606, the skin wash was monitored using a Geiger Counter. Any area demonstrating high levels of radioactivity was rewiped with gauze pads until the level of radioactivity was deemed acceptable. Please indicate what the acceptable level was and how it was determined.

Allergan Response: The Geiger counter is relatively insensitive to the ¹⁴C radioisotope, and it therefore provides a gross estimate of radioactivity levels. The Geiger counter was used in the R168-154-8606 study to assess for "hot spots" of residual gel on the skin surface, i.e., to find out if any areas were inadvertently missed during the washing process.

The procedure used was as follows: the Geiger counter was played above the skin surface with the scale set to the x10 sensitivity setting, then the washing procedure was performed, and the Geiger counter was again played above the surface at the x1 setting

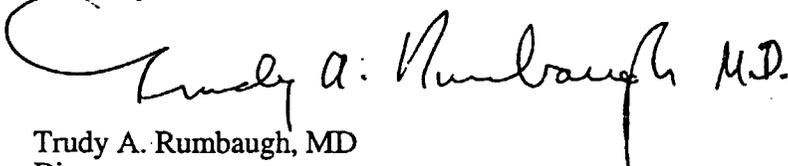
October 29, 1996
Cover Memo to Dr. Wilkin
NDA 20-600
Page 2 of 2

increased sensitivity). The "acceptable level" was a greater than drop in count rate, indicating that washing of the surface had occurred at that location. Thus, a qualitative judgment was made to verify that all areas had been wiped, as opposed to a quantitative indication of gel removal from the skin surface. During the study, no additional wiping was required following the x1 sensitivity Geiger counter check.

In addition, we are officially submitting the attached human blood and plasma pharmacokinetic samples stability data to NDA 20-600 that was previously faxed to Mr. Cross on October 9, 1996.

We ask that the information in this amendment be reviewed and filed to NDA 20-600, Tazorac™ Gel. If you have any further questions or require additional information please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,



Trudy A. Rumbaugh, MD
Director
Global Regulatory Affairs, Retinoids

TR/sm

ALLERGAN

ORIG AMENDMENT

5 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

BC



November 14, 1996

Jonathan Wilkin, MD
Acting Director,
Food and Drug Administration
Center for Drug Evaluation and Research/HFD-540
Division of Dermatologic and Dental Drug Products
9201 Corporate Blvd., Bldg. 2
Rockville, MD 20850



**REF: NDA 20-600: Tazorac™ (tazarotene) 0.05%, 0.1% Gels
Chemistry, Manufacturing and Controls (CMC) Amendment
Validated Analytical Procedure**

Dear Doctor Wilkin:

Allergan hereby amends the above-referenced NDA with a CMC amendment consisting of a Review and Archival copy of the validated Analytical Procedure for the Drug Product, Tazorac™ Gel. This analytical procedure was previously faxed to your Division. This is being sent in at the request of the Project Manager, Frank Cross, Jr.

We ask that this information be reviewed and retained in the file of NDA 20-600, Tazorac™ Gel. If you have any further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Thomas Walton / for

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

TR/tww

BM

November 18, 1996

Jonathan Wilkin, MD
Acting Director,
Food and Drug Administration
Center for Drug Evaluation and Research/HFD-540
Division of Dermatologic and Dental Drug Products
9201 Corporate Blvd., Bldg. 2
Rockville, MD 20850



**REF: NDA 20-600: Tazorac™ (tazarotene) 0.05%, 0.1% Gels
Clinical Information Amendment
Case Report Forms (CRFs) for Subjects Who Became Pregnant**

Dear Doctor Wilkin:

Allergan hereby amends the above-referenced NDA with a Clinical Information amendment consisting of a Review and Archival copy of the CRFs for patients who became pregnant during the clinical studies for Tazorac™ Gel. These CRFs were previously faxed to your Division. This amendment is being officially submitted at the request of the Project Manager, Frank Cross, Jr.

We ask that this information be reviewed and retained in the file of NDA 20-600, Tazorac™ Gel. If you have any further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

ALLERGAN

ORIGINAL



2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

November 26, 1996

Jonathan Wilkin, MD
Acting Director,
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

BL
NDA ORIG AMENDMENT



REF: NDA 20-600/Tazorac™ (tazarotene) 0.05%, 0.1% Gel
Response #2 to Proposed Draft Labeling received by Fax on November 21

Dear Doctor Wilkin:

Allergan hereby submits, to the above-referenced NDA, a review and archival copy of our response to the above-referenced proposed draft labeling. Our response reflects the most up-to-date information submitted by Allergan to the Agency and is in accordance with the labeling approved for the other marketed topical retinoids for acne and photoaging: Retin-A® (tretinoin), Renova® (tretinoin) and Differin® (adapalene). We have also sent a "Desk Copy" of this second response, by fax, to the Project Manager, Frank Cross, Jr.

We have enclosed both a tabular summary that compares the proposed draft labeling received with Allergan's recommended changes to the draft copy as well as a plain, revised draft with all revisions incorporated. We would welcome the opportunity to discuss this response.

Please note that the draft labeling provided today has comments on page 16: Pregnancy, and a Discussion Section B that did not appear with the document faxed to the Agency on November 25, 1996.

We ask that the enclosed labeling be reviewed and retained in the file of NDA 20-600, Tazorac™ Gel. If you should have any other questions or require additional information, please contact Thomas Walton at 714.246.4470, Pacific Time. I will return to the office on Tuesday, December 3.

Sincerely,

Thomas Walton (for)

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> MAIL <input type="checkbox"/> MEMO
CSO INITIALS	DATE

ALLERGAN

ORIGINAL

5 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500



December 2, 1996

NEW CORRESPONDENCE

Jonathan Wilkin, MD
Acting Director,
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



REF: NDA 20-600/Tazorac™ (tazarotene) 0.05%, 0.1% Gel
Draft Labeling on Diskette--WordPerfect® 6.1

Dear Doctor Wilkin:

Allergan hereby submits, to the above-referenced NDA, this letter which confirms our shipment of a desk copy of the proposed Draft Labeling on diskette to the Review Division for this NDA. This diskette is being sent at the request of the Project Manager, Frank Cross, Jr.

This diskette contains the proposed Draft Labeling submitted to the Division on November 26, 1996. The information on the diskette was originally constructed in Microsoft Word®. We have reviewed the conversion to WordPerfect® and have noted the following changes from the original, none of which are material to the textual portion:

- Certain schematics, including the Allergan logo and the molecular structure of tazarotene have been eliminated, due to conversion inconsistencies concerning the graphics interaction of the two word processing programs
- Pagination was not retained exactly as in the original
- There is a change to type size in some of the page headers.

The proposed Draft Labeling submitted in hard copy on November 26, 1996 is the master document, and, in the event of any discrepancy between the hard copy submitted and the diskette provided to Mr. Cross, the November 26 submission will take precedence. As always, we would welcome the opportunity for discussion of this labeling, at your convenience.

We ask that the enclosed labeling be reviewed and retained in the file of NDA 20-600, Tazorac™ Gel. If you should have any other questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Thomas Walton / for

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

December 4, 1996

BC

NDA ORIG AMENDMENT

Jonathan Wilkin, MD
Acting Director,
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



REF: NDA 20-600/Tazorac™ (tazarotene) 0.05%, 0.1% Gel
Labeling for Container/Closure Systems--New Drug Product

Dear Doctor Wilkin:

Allergan hereby submits, to the above-referenced NDA, a review and archival copy of our proposed labeling for the container/closure system and cartons for the new drug product. Previously we have faxed and supplied by courier identical copies of this material to the Project Manager, Frank Cross, Jr.

We ask that the enclosed container and carton labeling copy be reviewed and retained in the file of NDA 20-600, Tazorac™ Gel. If you should have any other questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

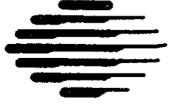
Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

ORIGINAL

ALLERGAN



35 DuPont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

December 5, 1996

BL
NDA ORIG AMENDMENT

Jonathan Wilkin, MD
Acting Director,
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
2301 Corporate Blvd., Building 2
Rockville, MD 20850



REF: NDA 20-600/Tazorac™ (tazarotene) 0.05%, 0.1% Gel
Official Submission of Proposed Labeling faxed on November 25, 1996

Dear Doctor Wilkin:

Allergan hereby submits, to the above-referenced NDA, a review and archival copy of the proposed Draft Labeling faxed to you on the evening of November 25, 1996. This official submission is in response to a request by the Project Manager, Frank Cross, Jr.

We ask that the enclosed labeling be reviewed and retained in the file of NDA 20-600, Tazorac™ Gel. If you should have any other questions or require additional information, please contact me at 714.246.4470 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

REVIEWS COMPLETED
DISPOSITION
<input type="checkbox"/> LETTER <input type="checkbox"/> INFO <input type="checkbox"/> ...
CSO INITIALS

ALLERGAN



2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

December 11, 1996

Jonathan Wilkin, MD
Acting Director,
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products/ HFD-540
9201 Corporate Blvd., Bldg. 2
Rockville, MD 20850

**REF: NDA 20-600: Tazorac™ (tazarotene) 0.05%, 0.1% Gels
Chemistry, Manufacturing and Controls (CMC) Amendment
Drug Product Registration Stability, 24-months
Drug Product Manufacturing Process Validation Stability, 12-months**

Dear Doctor Wilkin:

Allergan hereby amends the above-referenced NDA with a CMC amendment consisting of a Review and Archival copy of stability data for the New Drug Product, Tazorac™ Gel.

Based upon our continued monitoring of the Registration Stability batches and the Manufacturing Process Validation Stability batches, Allergan proposes, at least, a 24-month expiry dating for all tube sizes and for both concentrations for product stored up to 30° C (86° F). We may extend the expiry date, based on further monitoring, consistent with the stability protocol included in the original NDA.

A desk copy of this report has been forwarded to Sidney Gilman, Ph.D., in the Division of Medical Imaging and Radiopharmaceutical Drug Products, the acting chemistry reviewer for this NDA and the requestor for this data.

We ask that this information be reviewed and retained in the file of NDA 20-600, Tazorac™-Gel. If you have any further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

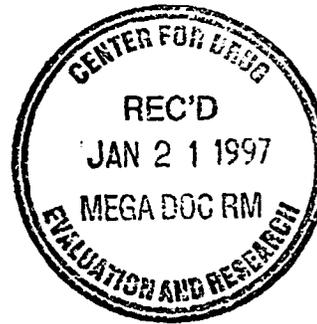
Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

January 17, 1997

Michael Weintraub, MD
Director, Office of Drug Evaluation V
Center for Drug Evaluation and Research/HFD-105
Food and Drug Administration
9201 Corporate Boulevard
Document Control Room
Rockville, MD 20850



REF: NDA 20-600/Tazorac™ (tazarotene gel) 0.05%, 0.1% Gels
Response to Approvable Action Letter dated December 30, 1996

Dear Doctor Weintraub:

Allergan is amending the above-referenced NDA with our response to the Approvable Action Letter dated December 30, 1996. This amendment contains information previously submitted in the original NDA and subsequent amendments, new information that will allow you to confidently assign a Pregnancy Category of "C," information to obtain the approval of Tazorac Gel 0.05% for facial non-inflammatory acne and a discussion of the proposed Phase 4 commitments.

Four copies of this two volume response have been provided to the agency: one archival copy, one review copy, and two desk copies (one for Frank Cross and one for Michael Weintraub). For the convenience of the agency, an electronic copy of the Draft Package Insert has also been provided. This can be found in the desk copy provided to the CSO, Frank Cross.

- We ask that this amendment be rapidly reviewed, as most data have been previously submitted. If you should have further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470.

Sincerely,

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

ALLERGAN

Mont Drive, P.O. Box 19554 Irvine CA 92623-9534 (714) 752-4500

ORIGINAL
NEW CORRESP

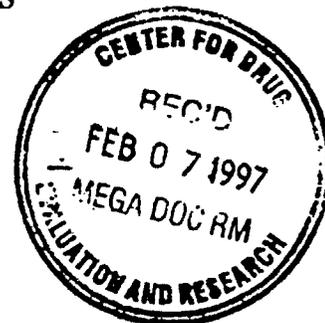
NC



FEB 05 1997

FEDERAL EXPRESS

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
HFD- 540
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, Building 2
Rockville, MD 20850



REF: NDA 20-600: Tazorac™ (tazarotene) 0.05%, 0.1% Gels
Electronic Version of Draft Package Insert

Dear Dr. Wilkin:

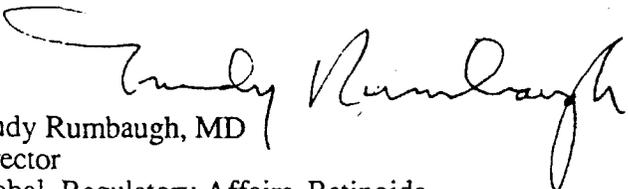
Allergan hereby submits, to the above referenced NDA, this letter which confirms our shipment of a desk copy of the proposed Draft Package Insert on diskette to the Review Division for this NDA via Project Manager, Frank Cross, Jr. per his telephone request of January 29, 1997.

The hard copy of the package insert was previously submitted to the NDA by Allergan in response to the FDA Approvable Action Letter on January 17, 1997. The document can be found under the Proposed Draft Labeling tab on Page 1 062 of the submission.

One of the files on the diskette (File name: wpdraftpi.doc) is in WordPerfect® 6.0, formatted for the Windows 95 program on PC. The other file (File name: w6draftpi.doc) contains the original version in Microsoft Word®, initially submitted in our January 17, 1997 correspondence. During the document conversion to WordPerfect, certain graphics may not reproduce exactly; however, all textual material should be exact. If there is any discrepancy between the hard copy and the diskette, the hard copy should be considered to be the official version.

We ask that the information in this amendment be reviewed and officially filed to NDA 20-600, Tazorac™ Gel. If you should have any additional questions or require further information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470.

Sincerely,


Trudy Rumbaugh, MD
Director
Global Regulatory Affairs, Retinoids

cc: Frank Cross, CDER Project Manager

ALLERGAN

ORIGINAL



2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534 (714) 246-6751 Fax: (714) 246-6987

Lester J. Kaplan, Ph.D.
Corporate Vice President
Science & Technology

February 25, 1997



Jonathan K. Wilkin, M.D.
Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products/HFD - 540
9201 Corporate Blvd., Bldg. 2
Rockville, MD 20850

HC
NEW CORRESP

REF: NDA 20-600: Tazorac (TM) (tazarotene) 0.05%, 0.1% Gels

Dear Dr. Wilkin:

I first want to thank you for arranging the telconference with the Allergan team last Wednesday, February 19, to discuss the agencies methodology for determining the relevant human systemic exposure levels for our topical retinoid Tazarotene. Also, we appreciate you taking the time to discuss your philosophical approach to the evaluation of safety margins with respect to animal toxicokinetic parameters.

During the development of Tazarotene, and since the NDA was filed in June of 1995, our team has attempted to work closely with the agency to assure a smooth and rapid review of the file. It has been our priority to provide rapid, high quality responses to all agencies questions.

My goal is to facilitate moving this file from approvable to approved as rapidly as possible. We have attempted to clearly outline our views on the remaining label issues. I recognize that the agency may not agree with all of our positions and I want to avoid a protracted debate.

As the final decision maker for our company on the product labeling, I am sure that any areas of disagreement can be rapidly and amicably resolved during the course of a one hour meeting. Therefore, I believe the most efficient way to move forward for both of our organizations is for you and I, or a small group, to meet immediately and finalize the labeling.

I would very much appreciate your consideration of my proposal. Also, if you have any alternative suggestions on how we can more rapidly move forward they will receive my immediate attention.

Thank you for your cooperation.

Sincerely,

LK/jp

cc: P. Kresel
B. Shepherd

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500

DUPLICATE



March 28, 1997

BMI
ORIG AMENDMENT

Jonathan Wilkin, MD
Acting Director,
Food and Drug Administration
Center for Drug Evaluation and Research/HFD-540
Division of Dermatologic and Dental Drug Products
9201 Corporate Blvd., Bldg. 2
Rockville, MD 20850

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

REF: NDA 20-600: Tazorac™ (tazarotene) 0.05%, 0.1% Gels
Clinical Information Amendment
Case Report Forms (CRFs) for Subjects Who Became Pregnant

Dear Doctor Wilkin:

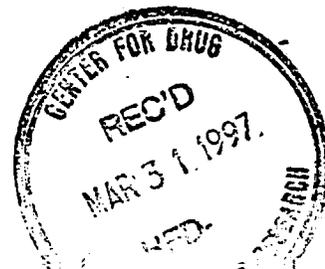
Allergan hereby amends the above-referenced NDA with a Clinical Information amendment consisting of a Review and Archival copy of the CRFs for 2 patients who became pregnant during the clinical studies for Tazorac™ Gel. This amendment is being officially submitted at the request of the Project Manager, Frank Cross, Jr.

Clinical Study # 190169-901-00 (Japan)
Subject

This subject delivered a healthy, full-term baby on December 27, 1996. No plasma sample was taken for Tazarotene or metabolite profiling

Clinical Study 190168-001
Subject

This subject delivered a healthy, full-term baby on January 25, 1997. A plasma sample taken indicates there was no detectable level of Tazarotene or metabolite present.



NDA 20-600
March 28, 1997
Pg. 2 of 2

We ask that this information be reviewed and retained in the file of NDA 20-600, Tazorac™ Gel. If you have any further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,



Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

ALLERGAN

7525 Dupont Drive, P.O. Box 19534, Irvine CA 92623-9534 (714) 752-4500



April 11, 1997

Bm
NDA ORIG AMENDMENT



Jonathan Wilkin, MD
Acting Director,
Food and Drug Administration
Center for Drug Evaluation and Research/HFD-540
Division of Dermatologic and Dental Drug Products
9201 Corporate Blvd., Bldg. 2
Rockville, MD 20850

**REF: NDA 20-600: Tazorac™ (tazarotene) 0.05%, 0.1% Gels
Clinical Information Amendment
Adverse Event Tables**

Dear Doctor Wilkin:

Allergan hereby amends the above-referenced NDA with a Clinical Information amendment consisting of a Review and Archival copy of Adverse Event Tables. This amendment is being officially submitted following an electronic mail request from Hon-Sum Ko, MD in March.

We ask that this information be reviewed and retained in the file of NDA 20-600, Tazorac™ Gel. If you have any further questions or require additional information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

REVIEW COMPLETE
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> MAIL <input type="checkbox"/> OTHER
CSO INITIALS
DATE

NATIONAL
PSORIASIS
FOUNDATION

NPF

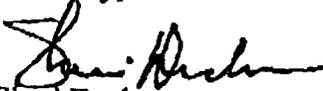
May 22, 1997

Ms. Gail Duner
Director of Marketing
Allergan Skin Care
2525 Dupont Drive
Irvine, CA 92713

Dear Ms. Duner:

The National Psoriasis Foundation (NPF) agrees to allow Allergan Skin Care to include information about the NPF as part of the patient package insert for the new psoriasis drug Tazorac. We appreciate this opportunity to acquaint people with our educational services.

Sincerely,


Sheri Decker
Associate Director