CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-600

ADMINISTRATIVE DOCUMENTS

Cross

NDA 20-600

JUN 6 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%.

We acknowledge receipt of your communications dated June 22, 28 (two) and 30, July 7, 10 and 26, August 11, September 21 and 22, October 17 and 30, and December 11, 1995; and January 9, February 5, 26 and 27, March 8, 18, 19, and 27, and April 25, 1996.

This new drug application provides for the treatment of acne vulgaris and plaque psoriasis.

We have completed our review of this application and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

The deficiencies may be summarized as follows:

Chemistry, Manufacturing, and Controls Issues

1. With regard to the description and characterization of the drug substance the information presented on page 3-029 is not sufficient to support the Please submit full details of the study using

2. Please provide the full address of the Allergan testing site that performs final release and stability testing of tazarotene bulk drug substance for

3. With regard to the synthesis/method of manufacture of the bulk drug substance manufactured at

   A. The list of components provided by for the manufacture of tazarotene bulk drug substance (BDS) is incomplete. A list of all components used in should be submitted for our evaluation When compiling a list of components, please include the quality or grade of the inactive component (i.e., USP, ACS, etc.).

   B. Please provide Certificates of Analysis of starting materials used by

   C. Please specify the identity testing that is performed for . In addition, please include the acceptance specifications for this starting material.

   D. Please provide the procedure used for the purification of at the facility. Please include GC and HPLC chromatograms along with the identification of impurities such as

   E. Please provide information to demonstrate that is a commercially available starting material used at both If it is not, please provide full details of the chemistry, manufacture, and control of this intermediate from commercially available starting material.

   F. The specification for the intermediate is not less than (NLT) % w/w. Please identify any impurities that form as byproducts or degradants , up to %.

G. Please identify the in-process tests used to detect the formation of the intermediate product,

H. Please identify any impurities that result from byproduct formation or degradation in the preparation of In general, we suggest that an impurity profile for synthesis of tazarotene be submitted.

I. Please state whether there are any other other identifiable peaks in the HPLC for In addition, please list other impurities besides the starting material that may be present at less than % with respect to

J. The proposal to increase the batch size of kg reaction scale to a kg reaction scale did not address procedures for the remaining steps. Please provide the rationale justifying the omission of the procedures.

K. We have concerns about the capability of the synthesis. We recommend that a batch be synthesized and analyzed and the data submitted for our evaluation.

L. In general, the broadness in yield at each synthetic step in the manufacture of at may imply that the consistency in control of the chemical reaction is still being evaluated. Please submit a tabular summary of reaction yields at each of the for at least 3 or more lots of for our evaluation.

M. The in-process introduces an unidentified standard Please identify the standard used. In addition, please provide the rationale explaining why the the retention times for crude tazarotene min), and purified tazarotene min), are different.

4. With regard to the bulk drug substance manufactured at the facility:

A. Please provide the numerical release specifications for purchased and purified

B. Please identify the impurities found in the GC chromatogram on page 6-271 for the synthesis of

C. Please provide tables for components and equipment for the formation of

D. The tests for which are used in of the tazarotene manufacturing process have been omitted by the facility. A commitment to add this control, with a specification of not more than ppm, to the release controls at the facility should be submitted.

5. With regard to the regulatory specifications/analytical method:

A. From the data reported, the melting point of tazarotene may not be a crucial release parameter when all the other supportive tests are considered. The change in the melting range specifications at the contract manufacturers and at the testing facility for release is not consistent. Efforts to abide by USP testing as stated in section 741 have resulted in the accommodation of the data to fit the specifications. We recommend that either you return to testing with differential scanning calorimetry (DSC) or that you formally withdraw this release control due to melting range variablility.

B. Data from for the HPLC weight assay has been reported in appendix 3.7.4D. Please provide the rationale for the omission of the information on the HPLC weight assay of tazarotene and related substances manufactured at the facility.

C. Prior to evaluating the method validation of the HPLC weight percent assay procedure for and related substances, the following information is requested:

i. The accuracy of the method for tazarotene and its impurities.

ii. Raw data for linearity and precision.

6. With regard to the container/closure system for storage:

In addition to the HPDE container, can secondary container has been used at the facility in stability studies for the tazarotene. This information was not presented as an additional secondary storage container in section 3.2.3.15. Please clarify if it will be an alternative secondary container for the drug substance at both the facilities.

7. With regard to the manufacturer of the drug product:

A. The testing facility for release and stability testing of the drug product at Allergan in Irvine, California, was not reported under manufacturing facilities. Please submit the full address and specific function of this facility for our review and evaluation.

B. If post-approval stability testing of tazarotene gel will be performed by Allergan (Ireland), please provide full details for drug product testing of the qualification lots.

C. Please submit a copy of an executed batch record for a primary stability batch.

8. With regard to the regulatory specifications/methods:

We suggest that additional test parameters for the in-process control of the drug product be reported in table 3.3.6.2-1 on page 3-182. Please submit in-process controls for tazarotene, related substance AGN 190299, and related substance .

9. With regard to the drug product stability:

A. Please clarify what batches of drug product, representative of active from both are assigned as qualification batches.

B. The inhomogeneity effect at 25°C/60%RH represents a significant problem in maintaining tazarotene gel stability for both formulations (8606X and 8607X-A) within the proposed specifications. It is our understanding that the proposed commercial size batch will be kg, while your previous stability studies have been performed on kg batches. At least 2 batches manufactured at a minimum of one tenth kg) the commercial size, combined with the kg batches, are required to establish the expiration dating period.

C. Assay values for tazarotene gel stored at 25°C/60%RH were found to be out of specification. Only selected data for the degradant profile were recorded (i.e., Table 123, page 9-340). No data for the other stability tests were recorded. Please submit all drug product stability data so that we may examine the inhomogeneity effect on the other test parameters.

Biopharmaceutics Issue

The stability of tazarotene and metabolite in biological samples should be tested at the concentration range similar to that found in the pharmacokinetic studies and clinical trials.

Microbiology Issues

1. Regarding the Preservative Effectiveness Testing (PET) and Microbial Limits Testing (MLT):

   A. Please provide the methods used for both the PET and MLT tests. If the tests are USP tests, this should be stated.

   B. Please provide numerical test results from the PET tests performed which demonstrate the effectiveness of the preservative system at the lowest concentration specification for the benzyl alcohol.

   C. Please provide the acceptance specifications for the Microbial Limits Tests. Specifications should be established for total aerobic count, total yeasts and molds, and absence of indicator pathogens.

2. Please describe any in-process programs and controls that will be used to control microbial quality of the bulk drug substance.

Clinical Issue

Differences in the formulations used in the pivotal trials were noted. As these may impact on the approvability of the drug product, please provide the qualitative and quantitative characteristics of the ingredients.

Pharmacology Issues

1. The following items are required to allow us to make a final judgment on the adequacy of the submitted dermal carcinogenicity and oral rodent toxicity studies:

   A. The dietary data set, including the weight gain and food consumption data, for both studies.

   B. A code book for the tumorigenicity data.

   C. Survival and onset data for the tumors.

Please submit all safety information you now have regarding your new drug, in accordance with the requirements of 21 CFR 314.50(d)(5)(vi)(b). Please provide updated information as listed below:

A. Retabulate all safety data, including results of trials that were still ongoing at the time of NDA submission. The tabulation should take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

B. Retabulate drop-outs with new drop-outs identified. Provide discussion where appropriate.

C. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

D. Provide details of any significant changes or findings, if any.

E. Summarize worldwide experience on the safety of this drug.

In addition, please update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events. The update should cover all studies worldwide and uses of the drug including:

A. Those involving indications not being sought in the present submission,

B. Other dosage forms, and other dose levels, etc.

We reserve comment on the proposed labeling for this drug product until its safety and effectiveness have been established. However, the proposed proprietary name for this drug product, "Zorac™" was judged to be unacceptable by the CDER Labeling and Nomenclature Committee.

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with good manufacturing practices (CGMP) is required before this application may be approved.

Athough not the basis of the non-approval action for this application, additional comments and requests for information will be provided to you in a separate communication.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, you may request an informal conference with the members of the Division of Dermatologic and Dental Drug Products to discuss in detail the issues associated with this application. The meeting is to be requested at least fifteen days in advance.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

The reviewers for this application consisted of:

Jonathan K. Wilkin, M.D., Division Director, DODDDP, HFD-540
Linda Katz, M.D., Deputy Division Director, DODDDP, HFD-540
Hon Sum Ko, M.D., Medical Officer, DODDDP, HFD-540
R. Srinvasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Steve Thomson, Ph.D., Biostatistician, DOBIV, HFD-725
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DODDDP, HFD-540
Hilary Sheevers, Ph.D., Toxicologist, DODDDP, HFD-540
Amy Nostrandt, D.V.M., Ph.D., Toxicologist, DODDDP, HFD-540
Eric Sheinin, Ph.D., Director, DNDCIII, HFD-830
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540
Sydney Gilman, Ph.D., Chemist, DNDCII, HFD-160
Dennis Bashaw, Ph.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Frank Pelsor, Ph.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Sue-Chih Lee, Ph.D., Biopharmaceuticist, DPEIII, HFD-880
Peter Cooney, Ph.D., Microbiology Supervisor, ONDC, HFD-160
Patricia Hughes, Ph.D., Microbiologist, ONDC, HFD-160
Maria Rossana R. Cook, M.B.A., Supervisory Project Manager, DODDDP, HFD-540
Frank Cross, MA, LCDR, Regulatory Management Officer, DODDDP, HFD-540

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
HFD-613
HFD-638
HFD-540/Derm File
HFD-540/MO/Ko
HFD-160/CHEM/Gilman/5.1.96
HFD-160/MICRO/Hughes/5.28.96
HFD-540/PHARM/Nostrandt/5.28.96
HFD-725/BIOSTAT/Thomson/5.30.96
HFD-880/BIOPHARM/Lee/5.28.96
HFD-540/PROJ MGR/Cross
Concurrence:
HFD-540/DIV DIR/Wilkin/6.4.96
HFD-540/DEP DIR/Katz/5.31.96
HFD-830/DIV DIR/Sheinin/6.6.96
HFD-540/CHEM SUPV/DeCamp/5.27.96
HFD-540/PHARM SUPV/Jacobs/5.28.96
HFD-160/SUPV MICRO/Cooney/5.28.96
HFD-880/BIOPHARM SUPV/Bashaw/5.28.96
HFD-725/BIOSTAT SUPV/Srinivasan/5.30.96
HFD-540/PROJ MGT SUPV/Cook/5.27.96
HFD-540/PM/Cross/6.4.96
fhc/rev1-5.9.96/rev2-5.16.96/rev3-5.21.96/rev4-5.28.96/rev5-5.30.96
/rev6-5.31.96/rev7-6.4.96/rev8-6.6.96
mrrc/rev4-5.23.96
NOT APPROVABLE

United States Patent [19]

Chandraratna

[11] Patent Number: 5,023,341

[45] Date of Patent: Jun. 11, 1991

[54] COMPOUNDS HAVING A DISUBSTITUTED ACETYLENE MOIETY AND RETINOIC ACID-LIKE BIOLOGICAL ACTIVITY

[75] Inventor: Roshantha A. S. Chandraratna, El Toro, Calif.

[73] Assignee: Allergan, Inc., Irvine, Calif.

[21] Appl. No.: 409,477

[22] Filed: Sep. 19, 1989

[51] Int. Cl.[5] C07D 335/06

[52] U.S. Cl. 549/23

[58] Field of Search 546/164; 549/23

[56] References Cited

U.S. PATENT DOCUMENTS

4,739,098	4/1988	Chandraratna	560/8
4,810,804	3/1989	Chandraratna	514/311

FOREIGN PATENT DOCUMENTS

0176034	4/1986	European Pat. Off. .
3706060	9/1987	Fed. Rep. of Germany .

OTHER PUBLICATIONS

A General Synthesis of Terminal and Internal Arylalkynes by the Palladium-Catalyzed Reaction oof Alkynylzinc Reagents with Aryl Halides, by Anthony O. King and Ei-ichi Negishi, *J. Org. Chem.* 43 1978, p. 358.

A Convenient Synthesis of Ethynylarenes and Diethynylarenes, by S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* 1980, pp. 627-630.

Conversion of Methyl Ketones into Thermal Acetylenes and (E)-Trisubstituted Olefins of Terpenoid Origin, by Ei-ichi, Anthony O. King, and William L. Klima, *J. Org. Chem.* 45 1980, p. 2526.

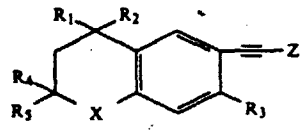
Primary Examiner—Frederick E. Waddell

Assistant Examiner—Raymond Covington

Attorney, Agent, or Firm—Gabor L. Szekeres; Martin A. Voet; Robert J. Baran

[57] ABSTRACT

Disubstituted acetylene thiochroman containing derivatives of the formulae below wherein the symbols have the following meanings; R_1, R_2, R_3, R_4 and R_5 are hydrogen or lower alkyl groups (of 1-6 carbons) where R_1, R_2, R_3, R_4 and R_5 may be identical or different from one another) X is S



9 Claims, No Drawings

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-600 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: tazarotene gel, 0.05%, 0.1% Action: AP AE (NA)

Applicant Allergan Therapeutic Class 1S

Indication(s) previously approved None

Pediatric labeling of approved indication(s) is adequate ____ inadequate ____

Indication in this application _____

(For supplements, answer the following questions in relation to the proposed indication.)

____ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

✓ 6/3/96 **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

____ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

____ b. The applicant has committed to doing such studies as will be required.
- ____ (1) Studies are ongoing,
- ____ (2) Protocols were submitted and approved.
- ____ (3) Protocols were submitted and are under review.
- ____ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

____ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

Waiver Line

____ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

____ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

PM 5/21/96

Signature of Preparer and Title (PM, CSO, MO, other) Date

gmk 5/21/96

6/3/96

cc: Orig NDA/PLA # 20-600
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-600 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF 0-540 Trade (generic) name/dosage form: tazarotene gel, 0.05% 0.1% Action: AP AE NA

Applicant Allergan, Inc. Therapeutic Class 1S

Indication(s) previously approved None

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Acne vulgaris, Plaque psoriasis

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

X 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

F. Miller, MA, CCRP, Project Manager — 10/22/96

Signature of Preparer and Title (PM, CSO, MO, other) — Date

cc: Orig NDA/PLA # 20-600
HF 0-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

12/9/96

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-600 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Tazorac (Tazarotene) Gel, 0.05%, 0.1% Action: (AP) AE NA

Applicant: Allergan, Inc. Therapeutic Class 1S

Indication(s) previously approved None

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Acne vulgaris, Plaque psoriasis

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

X 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

[signature] M.A., LCDR, Regulatory Management Officer 4/4/97

Signature of Preparer and Title (PM, CSO, MO, other) Date

6/11/97

cc: Orig NDA/PLA # 20-600
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

ALLERGAN

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

CERTIFICATION

ALLERGAN, INC., HEREBY CERTIFIES THAT NEITHER ALLERGAN, INC. NOR ANY PERSON EMPLOYED BY ALLERGAN, INC. HAS BEEN DEBARRED UNDER SECTION 306(a) OR 306(b) OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT, AS AMENDED, AND THAT NO DEBARRED PERSON WILL, IN THE FUTURE, BE EMPLOYED BY ALLERGAN, INC. IN CONNECTION WITH ANY APPLICATION FOR APPROVAL OF A DRUG BY THE FOOD AND DRUG ADMINISTRATION

Peter Kresel Dated June 12, 1995

Peter Kresel, MS, MBA
Vice-President
Global Regulatory Affairs

Executive CAC
October 8, 1996

Committee members: Joseph DeGeorge, Ph.D., Chair (HFD-024)
Joseph Contrera, Ph.D.
Charles Resnick, Ph.D., Rotating member (HFD-110)
Abby Jacobs, Ph.D., Team Leader (HFD-540)
Sharon Olmstead, Exec Sec (HFD-006, non-voting member)

NDA 20-600 (Nostrandt; HFD-540)
Tazarotene Gel
Allergan

The sponsor submitted carcinogenicity study results from a long term (88 weeks) topical administration mouse study using doses of 0, 0, 0.05, 0.125, 0.25, and 1.0 (reduced to 0.5 mg/kg in males) mg/kg/day. The dose selection was based on MTD in the 13-week toxicity study. Dose limiting toxicity was corrosive irritation caused by the topical application of the drug product. Vehicle used in the carcinogenicity study was the same as that used in the human clinical trials. The sponsor reported no significant tumor findings in carcinogenicity study in either males or females.

The committee concurred with the dose selection and study design. The findings were adequately addressed by historic and control range findings.

Joseph DeGeorge, Ph.D.
Chair, CAC

concur: JDeGeorge/10.25.96

cc: NDA file
Division file
HFD-540/AJacobs/ANorstandt
CAC file

Signatory authority signed all copies

DEPARTMENT OF HEALTH & HUMAN SERVICES

DEC 19 1996

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: December 3, 1996

To: Jonathan Wilkin, M.D.
Director, DTDP, HFD-540

From: Wilson H. De Camp, Ph.D.
Chemistry Team Leader, HFD-830

Subject: Team Leader's Addendum, Chemist's Review #3, NDA 20-600, tazarotene gel

In addition to the items reviewed with this submission, the following internal supporting documents have been received:

1. Response of the Labeling and Nomenclature Committee, dated 4/26/96, finding the proposed trade name of "Zorac" (proposed in the firm's submission of 3/18/96) unacceptable.
2. Response of the Labeling and Nomenclature Committee, dated 10/18/96, finding the proposed trade name of "Tazorac" (proposed in the firm's submission of 9/4/96) acceptable, and an alternate name of "Suretin" acceptable with reservations.
3. Response from the Office of Compliance to EER #8450 (submitted 7/5/95), finding that all facilities were in acceptable GMP compliance as of 8/9/96. This conclusion will support an approval action through 8/9/97.
4. EA review and signed FONSI, both dated 10/31/96.

Items 1-3, plus the signed FONSI, are attached for reference.

Wilson H. De Camp, Ph.D.
12/3/96

cc: Orig: NDA 20-600
HFD-540 (Division file, NDA 20-600)
HFD-541/Cross
HFD-540/Ko
HFD-540/Pharm
HFD-160/Gilman
N20600R3.MEM:whd, 12/3/96

12/19/96

(585)
#1

Request For Trademark Review

To: Labeling and Nomenclature Committee
Attention: John Grace, Vice Chair (HFD-810), MPN II

From: Division of DMIRP 18B-08 HFD-160
Attention: Syd Gilman Phone: 443-1560

Date: 19 March 1996

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

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

Established Name, including dosage form: TAZAROTENE 0.05%/0.1% TOPICAL GELS

Other Trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy):
topical treatment of plaque psoriasis and the the topical treatment of acne vulgaris

Initial comments from the submitter (concerns, observations, etc.):
A label is attached for your review.

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible

Consult #585 (HFD-160)

ZORAC tararotene 0.05 and 0.1% gels

The LNC found numerous look alike/sound alike conflicts with the proposed proprietary name: XERAC, ZIAC, SERAX, ZOVIRAX, and ZANTAC. SERAX, ZIAC and ZANTAC are all oral solids and present little potential for conflict however, XERAC and ZOVIRAX are both topicals and have a high potential for confusion.

The LNC finds the proposed proprietary name unacceptable.

W Bowne 4/26/96, Chair
CDER Labeling and Nomenclature Committee

#2

Consult #670 (HFD-540)

TAZORAC
ZOAC
ZRC
SURETIN — tazarotene gel 0.05 and 0.1%

The Committee feels that the proposed names ZOAC and ZRC are unacceptably close to ZIAC, an already marketed antihypertensive. The LNC found no look-alike/sound-alike conflicts with the names TAZORAC and SURETIN. The Committee was concerned that SURETIN might be used in advertising as "a sure thing" and this be misleading.

Overall, the Committee found ZOAC and ZRC unacceptable, TAZORAC acceptable and SURETIN acceptable with concerns.

D C Boring 10/18/96, Chair
CDER Labeling and Nomenclature Committee

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: June 11, 1997

JUN 11 1997

To: Jonathan Wilkin, M.D.
Director, DDDDP, HFD-540

From: Wilson H. De Camp, Ph.D.
Chemistry Team Leader, HFD-830

Subject: NDA 20-600, Tazorac (tazarotene) Topical Gel, 0.05 and 0.1%, Chemist's Review #5 (amended)

The subject review, originally completed 3/17/97, was amended 4/8/97 to clarify the nature and extent of the phase 4 commitments. This amendment followed a telephone conversation on 4/2/97 (minutes attached), in which the applicant agreed to the commitments as stated in Chemist's Review #5. A copy of the telecon minutes was omitted from Dr. Gilman's review, since it was not available to him at the time of his amended review. In addition, these minutes did not emphasize the added clarification that the scale-up of bulk manufacture only applied to the facility, hence the omission of the facility from the phase 4 commitment in review #5. This point is, however, noted in Dr. Gilman's review (amendment, pg. 3, "FDA Comment", 2nd paragraph).

The commitments should be acknowledged in the approval letter as stated in Dr. Gilman's review.

It should also be noted that his review also misspells the trade name of the drug; it should be Tazorac.

Wilson H. De Camp, Ph.D.

att: memorandum, FCross, 4/8/97

cc: Orig: NDA 20-600
HFD-540 (Division file, NDA 20-600)
HFD-541/Cross
HFD-541/Cintron
HFD-540/Ko
HFD-540/Pharm
HFD-160/Gilman
N20600R5.MEM:whd, 6/11/97

JW 6/11/97

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) 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.

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