CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-600

APPROVAL LETTER

NDA 20-600

JUN 13 1997

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 Tazorac™ (tazarotene topical gel), 0.05% and 0.1%.

Please refer to our Not Approvable letter dated June 6, 1996, and our Approvable Letter dated December 30, 1996.

We acknowledge receipt of your amendments and correspondence dated January 2 and 17, February 5 and 25, March 17, 18, and 28, April 11, and May 28, 1997. The User Fee Goal date for this application is July 21, 1997.

This new drug application provides for the topical treatment of patients with stable plaque psoriasis of up to 20% body surface area involvement and topical treatment of patients with facial acne vulgaris of mild to moderate severity.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed final version of the labeling. Accordingly, the application is approved effective upon the date of this letter.

The final printed labeling (FPL) must be identical to the attached revised labeling . The attached revised labeling was stated to be acceptable to you in the facsmile of your letter dated June 10, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit twenty copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar

material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-600. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated January 17, March 17, 1997, and in the facsimiles of your letters dated June 11, 1997. These commitments, along with any completion dates agreed upon, are listed below:

Clinical protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to

this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Frank H. Cross, Jr., M.A., LCDR
Regulatory Management Officer
(301) 827-2020

Sincerely yours,

M Weintraub 6/13/97

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

Enclosure

The reviewers for this application consisted of:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Linda Katz, M.D., Deputy Division Director, DDDDP, HFD-540
Hon-Sum Ko, M.D., Medical Officer, DDDDP, HFD-540
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Steve Thomson, Ph.D., Biostatistician, DOBIV, HFD-725
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Hilary Sheevers, Ph.D., Toxicologist, DDDDP, HFD-540
Amy Nostrandt, D.V.M., Ph.D., Toxicologist, DDDDP, 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
Sue-Chih Lee, Ph.D., Biopharmaceuticist, DPEIII, HFD-880
Peter Cooney, Ph.D., Microbiology Supervisor, ONDC, HFD-805
Patricia Hughes, Ph.D., Microbiologist, ONDC, HFD-805
Maria Rossana R. Cook, M.B.A., Supervisory Project Manager, DOTCDE, HFD-560
Mary Jean Kozma-Fornaro, R.N., M.S.A., Supervisory Project Manager, DDDDP, HFD-540
Frank Cross, Jr., M.A., LCDR, Regulatory Management Officer, DDDDP, HFD-540

cc:
Original NDA 20-600
HFD-540/Division File (with draft labeling)
HFD-105/Weintraub (with draft labeling) MW 6/13/97
HFD-2/Lumpkin (with draft labeling)
HFD-735 (with draft labeling)
HFD-92 (with draft labeling)
HFD-222 (with draft labeling)
District Office (with draft labeling)
HF-2/Medwatch (with draft labeling)
HFD-40/ (with draft labeling)
HFD-613 (with draft labeling)
HFD-540/MO/Ko (with draft labeling) H.K. 6-11-97
HFD-160/CHEM/Gilman (with draft labeling)
HFD-160/MICRO/Hughes (with draft labeling)
HFD-540/PHARM/Nostrandt (with draft labeling) DCN 6/11/97
HFD-725/BIOSTAT/Thomson (with draft labeling) JFT 6/11/97
HFD-880/BIOPHARM/Lee (with draft labeling) SLC 6/11/97
HFD-540/PROJ MGR/Cross (with draft labeling)

Concurrence:

HFD-540/PROJ MGT SUPV/Kozma-Fornaro (with draft labeling)
HFD-540/ACTING DERM TL/Cook (with draft labeling)
HFD-880/BIOPHARM TL/Bashaw (with draft labeling) EB 6/12/97
HFD-540/CHEM TL/DeCamp (with draft labeling) WJ 6/11/97
HFD-540/PHARM TL/Jacobs (with draft labeling) a.j. 6/11/97
HFD-725/BIOSTAT TL/Srinivasan (with draft labeling) RS 6/11/97
HFD-830/DIV DIR/Chen (with draft labeling) CBC 6/13/97
HFD-540/DIV DIR/Wilkin (with draft labeling) GW 6/11/97
HFD-105/Walling (with draft labeling)
HFD-540/PM/Cross (with draft labeling)

drafted: oc/June 10, 1997/n20600a.ap
r/d Initials: OC
Final:

APPROVAL
PHASE 4 COMMITMENTS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-600

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-600

Food and Drug Administration
Rockville MD 20857

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

DEC 30 1996

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 Tazorac (tazarotene gel) Topical Gel, 0.05% and 0.1%.

Please refer to your Not Approvable letter dated June 6, 1996.

We acknowledge receipt of your amendments and correspondence dated June 27, and 28, July 11, 22, and 30, September 4, and 18, October 18, and 29, November 14, 18, and 26, December 2, 4, 5, and 11, 1996.

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

We have completed the review of this application as submitted with the draft labeling of June 22, 1995. Tazarotene gel, 0.05%, is approvable for the daily topical treatment of stable plaque psoriasis covering not more than 20% of body surface area. Tazarotene gel, 0.1%, is approvable for the daily topical treatment of stable plaque psoriasis covering not more than 20% of body surface area and in the treatment of mild to moderate facial acne vulgaris. Before this application may be approved, however, it will be necessary for you to submit the following information:

1. Revised draft labeling identical in content to the enclosed draft labeling. The proposed Tradename, Tazorac, for this drug product, was found acceptable.

2. Although study R168-146-8606, a phase 3 trial being conducted in the U.K., has not been unblinded, available safety data is needed.

3. The Study Report for R168-722-8606 has been submitted previously. The only additional information in this submission was a Table of ALL adverse events shown in the Safety Update (Safety Update Table 2c from 6/27/96 submission, p. 1-050). The data from the table does not agree with that in the study report (Table 8 of study report, p. 4-069 of 6/27/96 submission). The differences should be explained.

4. In R168-128-8606, documentation of an allergic component was not presented. You subsequently argued that the reactions represent local irritation produced by tazarotene gel. However, this is still classified as an allergic contact dermatitis in the data analysis. A correction of this is needed.

5. An analysis is needed of the age subsets within those patients less than 45 years of age in acne studies.

6. 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. In addition, plasma drug levels from subject in Study R168-221-8606 taken when pregnancy was discovered should be presented.

7. Please submit a commitment to conduct the following Phase 4 Study within 6 months of an Approval Letter:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the submission also submitted to the NDA.

Should an IND not be required to meet your Phase 4 commitment, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to Phase 4 commitments must be clearly designated "Phase 4 Commitments."

8. Please submit a commitment to provide the following:

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

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

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

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

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

5. 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.

Please also 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 and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

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 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Frank H. Cross, Jr., M.A., LCDR
Project Manager
Telephone: (301) 827-2020

Sincerely yours,

MWeintraub 11/3/96

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

Enclosure

The reviewers for this application consisted of:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
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