CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-184/002

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-184/S-002

Allergan, Inc.
Attention: Trudy Rumbaugh, M.D.
Director, Global Regulatory Affairs
2525 Dupont Drive
P. O. Box 19534
Irvine, California 92623-9534

Dear Dr. Rumbaugh:

Please refer to your supplemental new drug application dated June 28, 2001, received June 29, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AVAGE™ (tazarotene) Cream, 0.1%.

The July 29, 2002, submission received July 30, 2002, constituted a complete response to our April 29, 2002, approvable action letter.

In addition, we acknowledge receipt of your submissions dated May 13 and 14, June 24, July 2, 26 and 29, August 20 and 22, September 18 and 24, (electronic-mail), and September 24, 25 and 26, 2002 (facsimile).

This supplemental new drug application proposes the use of AVAGE™ (tazarotene) Cream, 0.1%, as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs.

We have completed the review of this supplemental application, as amended, 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 agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert and patient package insert). The carton and container will be revised and submitted to the agency as agreed via teleconference of September 25, 2002.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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 "FPL for approved supplement NDA 21-184/S-002."

Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments:

1. A commitment to summarize in each annual report all cases of lentigo maligna or melanoma that were exposed to topical tazarotene or are attributed to treatment with topical tazarotene.

2. A commitment to submit all medication error reports, both potential and actual, that occur with the drug Avage for a period of two years following the date of drug approval. Potential errors include any reports of potential circumstances or events that have the capacity to cause error and should be reported in each quarterly summary. Actual errors include any preventable event that reached the patient and caused harm, reached the patient and did not cause harm, and errors that did not reach the patient, such as if the wrong drug was prepared but system checks prevented the drug from reaching the patient or being administered to the patient. All actual errors should be submitted as a 15-day report regardless of patient outcome. A name change could be requested following the receipt of two actual errors that resulted in the wrong drug being administered due to proprietary name confusion.

If needed, submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

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.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for pediatric patients 17 years of age and younger.

In addition, please submit three copies of the introductory promotional materials 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 materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product 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 call Kalyani Bhatt, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

/s/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

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/s/

Jonathan Wilkin
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APPLICATION NUMBER

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Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-184/S-002

Allergan, Inc.
Attention: Trudy Rumbaugh, M.D.
Director, Global Regulatory Affairs
2525 Dupont Drive
P. O. Box 19534
Irvine, California 92623-9534

Dear Dr. Rumbaugh:

Please refer to your supplemental new drug application dated June 28, 2001, received June 29, 2001 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tradename (tazarotene) Cream, 0.1%.

We acknowledge receipt of your submissions dated October 30, 2001; January 21, February 19, April 15, and 25, 2002.

This supplemental new drug application proposes the use of Tradename (tazarotene) Cream, 0.1% for

We have completed the review of this application, as amended, and it is approvable. Please submit draft labeling revised in accordance with the enclosed labeling (text for the package insert, patient package insert, immediate container and carton labels). Further discussions regarding the labeling may be necessary.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDAs by submitting all safety information you now have regarding your new drugs. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. 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.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Kalyani Bhatt, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

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/s/

Jonathan Wilkin
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/s/

Jonathan Wilkin
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48 pages redacted from this section of the approval package consisted of draft labeling