CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-184/002

Correspondence

SE1-002/BL

ALLERGAN

5 Dupont Drive, P O Box 19534, Irvine California, USA 92623-9534 Telephone: (714) 246-4500 Website www.allergan.com

August 22, 2002

ORIGINAL

RECEIVED

AUG 23 2002

NDA SUPPL AMENDMENT

MEGA/CDER

Jonathan Wilkin, MD,
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd, Building 2
Rockville, MD 20850

REF: TRADENAME (tazarotene) Cream, 0.1%
NDA 21-184/S-002
Response to Teleconference Discussion--Labeling (August 15, 2002)

Dear Doctor Wilkin:

Allergan is responding to the labeling teleconference discussion between the Division of Dermatologic and Dental Drug Products and Allergan for the above referenced NDA/Supplement. As always, we appreciate opportunities for scientific and regulatory exchange. The modifications to the label are listed by label section.

TRADENAME:

Following FDA's feedback to the proposed tradenames submitted by Allergan in July and following the discussions with the Division, Allergan proposes the following tradename:

AVAGE (tazarotene) Cream, 0.1%.

A comprehensive rationale for this tradename selection was detailed in our August 20, 2002 submission to this NDA/Supplement.

PHASE 4 COMMITMENT:

Allergan commits to communicate to FDA via the Periodic Adverse Drug Experience Report a listing of all cases of lentigines which, upon further examination, are ultimately diagnosed as lentigo maligna melanomas.

CLINICAL PHARMACOLOGY:

The mechanism of action has been changed to include fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines.

ORIGINAL

CLINICAL STUDIES:

The study parameters are now listed as fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines.

Dr. Luke suggested that Allergan mention that non-Caucasians did not respond as well as Caucasians. However, the pooled study data for Caucasians and non-Caucasians (Asian, Hispanic and others) showed that in both groups a greater proportion of patients randomized to drug exhibited clinical improvement in facial wrinkling and mottled hyperpigmentation than in those treated with vehicle (references: ISE section 8.7.6.3, Tables 8.7.9.1 – 36 and 8.7.9.1 – 39). The logistic regression analyses indicated no statistically significant difference between racial groups, nor was there a statistically significant interaction between treatment and racial group.

The time to onset of significant improvement from baseline for benign facial lentigines has been added.

In response to the discussions concerning the experience of patients on long-term therapy, we have added the experience of the patients in the open-label phase of the pivotal trial (190168-033C) that studied patients up to 52-weeks.

INDICATIONS AND USAGE:

This section has been modified to include the parameters fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines throughout this section.

We have added that Tradename "does not Prevent or Eliminate...." rather than just "does not Eliminate...."

The third bullet point adds lentigo maligna to the conditions for which safety and efficacy has not been demonstrated.

CONTRAINDICATIONS:

This section has been modified to include the parameters fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines throughout.

The number of patients who became pregnant in topical tazarotene clinical studies was updated to thirteen and number who were found to be on vehicle has been updated to four.

PRECAUTIONS:

This section has been modified to include the parameters fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines throughout.

The following statement has been added:

[

]

INFORMATION FOR PATIENTS:

The statement that Tradename "does not prevent or remove wrinkles...." has replaced —

PEDIATRIC USE/GERIATRIC USE/ADVERSE REACTIONS:

These sections have been modified to include the parameters fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines.

DOSAGE AND ADMINISTRATION:

We have added the following statement:

"The duration of the mitigating effects on facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines following discontinuation of TRADENAME™ (tazarotene) Cream 0.1% has not been studied."

PATIENT PACKAGE INSERT:

This section has been modified to include the parameters fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines.

The following has been added to more completely explain the indications:

[

]

The following caution has also been added:

]

[

We ask that this labeling response be reviewed expeditiously in conjunction with our tradename submission of August 21, 2002 and filed to NDA 21-84/S-002. During my family leave, should you have any questions or require further information, please contact Thomas Walton at 714.246.4470 or Peter Kresel at 714.246.6781, Pacific Time.

Sincerely,

Thomas Walton for

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

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ALLERGAN	8/22/2002
TELEPHONE NO. *(Include Area Code)* 800-347-4500	FACSIMILE (FAX) Number *(Include Area Code)* 714.246.4272
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State. ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-184

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Tazarotene (USAN)	Tazorac®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate	AGN 190168

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AUG 2 3 2002
MEGA/CDER

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.05% 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Treatment of plaque psoriasis; Treatment of acne vulgaris;

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ■ OTHER

REASON FOR SUBMISSION Labeling

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ORIGINAL

13 pages redacted from this section of the approval package consisted of draft labeling

LERGAN

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August 20, 2002

DUPLICATE

RECEIVED
AUG 2 2 2002
MEGA/CDER

Jonathan Wilkin, MD,
Director,
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HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd, Building 2
Rockville, MD 20850

SE1-002 NC
EW CORRESP

REF: TRADENAME (tazarotene) Cream, 0.1%
NDA 21-184/S-002
Response to Teleconference Discussion--Tradename (August 15, 2002)

Dear Doctor Wilkin:

Allergan is responding to the teleconference discussion between the Division of Dermatologic and Dental Drug Products and Allergan for the above referenced NDA/Supplement. As always, we appreciate opportunities for scientific and regulatory exchange. In accordance with your suggestion we are forwarding one, final tradename proposal that we believe will mitigate the concerns expressed by the Office of Drug Safety, and others. The information on the other aspects of the label discussions will be submitted shortly. This tradename submission is in furtherance of ODE V decision of July 20, 2002, concerning Allergan's request for an alternative tradename through the Center's Formal Dispute Resolution Process.

Following FDA's feedback to the proposed tradenames submitted by Allergan in July and the discussions with your Division, we find that although we cannot accept [redacted] as you suggested, we propose the following, similar tradename:

AVAGE —

The concerns expressed were that AVAGE could have some resemblance in written prescription form, that could possibly confuse it with AMARYL® (glimepiride) Tablets or AMERGE® (naratriptan) Tablets.

The incidences of confusion with the written form will be negated by the suffix ' — would stand for ' —

It should be noted that both AMARYL® and AMERGE® have *completely different dosage forms, completely different container/closure systems, completely different routes of administration* and *completely different indications* from AVAGE Cream. AMERGE® is indicated for the oral treatment of acute migraine. AMARYL® is indicated as an oral blood glucose-lowering agent.

Therefore, the name AVAGE would bear no relationship to AMARYL® or AMERGE®, either phonetic or written. Further, there is no visual relationship physically (topical cream in an aluminum tube vs. tablets in bottles and unit-dose cartons [AMARYL®] or tablets in blister packs [AMERGE®]) between the AMERGE/AMARYL dosage forms and our product. In fact, the rationale that allowed both AMARYL® Tablets and AMERGE® Tablets to safely be approved with no significant health risks, even though both are remarkably similar in name, dosage form and route of administration, speaks very favorably to the approval of the AVAGE tradename for a topical cream. In the spirit of cooperation, Allergan would also thoughtfully consider other suffix designations that FDA might suggest as long as it preserves the AVAGE tradename root and does *not* introduce TAZORAC®.

Further, as you agreed, AVAGE was certainly the one submission that you found least objectionable and we have spent considerable time and resources clearing this name through the appropriate legal channels.

We ask that our revised proposal for settlement of the tradename issue be reviewed promptly. Allergan continues to believe that in the true spirit and intent of the Formal Dispute Resolution Process, a Division-level decision approving one alternate tradename should be forthcoming without further unnecessary delay. If the Division strongly believes otherwise and has decided not to implement the Formal Dispute Resolution Process decision, please advise us, so that we may seek the immediate and necessary legal (OCC) and CDER Director review, including requesting examination of the matter by the CDER Office of the Ombudsman. Certainly, we would hope such further action would be unnecessary and that as we always have in the past, be able to reach an acceptable compromise with the Division so that we can quickly gain approval for this important treatment.

We ask that this response be filed to NDA 21-184/S-002. During my family leave, should you have any questions or require further information, please contact Thomas Walton at 714.246.4470 or Peter Kresel at 714.246.6781, Pacific Time.

Sincerely,

Thomas Walton /for

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

ALLERGAN

2 Dupont Drive P O Box 19534, Irvine California, USA 92623-9534 Telephone (714) 246-4500 Website. www.allergan.com

July 29, 2002

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540, Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd, Building 2
Rockville, MD 20850

ORIGINAL

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REF: TRADENAME (tazarotene) Cream, 0.1%
NDA 21-184/S-002
Response to Approvable Action Letter Complete

NEW CORRESP

Dear Doctor Wilkin:

Allergan is reporting to you that we have completed all responses to the Approvable Action Letter and Dispute Resolution Process for the above-referenced NDA/Supplement.

- Safety Update, Foreign Labeling and Worldwide Distribution information was submitted on June 24, 2002
- Three proposed tradenames [redacted]AVAGE) were submitted on July 2, 2002.
- Response to the Allergan/FDA Labeling Teleconference was submitted on July 26, 2002.

We ask that the information in this letter and the information previously submitted be reviewed and maintained in the file of NDA 21-184. During my family leave, should you require further information, please contact Thomas Walton at 714.246.4470 or Peter Kresel at 714.246.6781, Pacific Time.

Sincerely,

Thomas Walton for

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

TR/tww

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ALLERGAN	7/29/2002
TELEPHONE NO. *(Include Area Code)* 800-347-4500	FACSIMILE (FAX) Number *(Include Area Code)* 714.246.4272

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State. ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-184

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Tazarotene (USAN)	Tazorac®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate	AGN 190168

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.05% 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Treatment of plaque psoriasis; Treatment of acne vulgaris;

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
■ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Response to FDA Request for Information

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

RECEIVED
JUL 30 2002
MEGA/CDER

ALLERGAN

Dupont Drive P O Box 19534, Irvine California USA 92623-9534 Telephone (714) 246-4500 Website: www.allergan.com

July 26, 2002

NDA SUPPL AMEND
S01-002/BL

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540, Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd, Building 2
Rockville, MD 20850

RECEIVED
JUL 29 2002
MEGA/CDER

REF: TRADENAME (tazarotene) Cream, 0.1%
NDA 21-184/S-002
Response to Teleconference Discussions (July 15, 2002)

Dear Doctor Wilkin:

Allergan is responding to the teleconference discussion between your Division and Allergan for the above referenced NDA/Supplement. As always, we appreciate opportunities for scientific and regulatory exchange. This response consists of the labeling with the modifications we believe were agreed upon by both parties. Also, we have included the Patient Package Insert separately for review by the Office of Drug Safety. Lastly, we are anticipating a positive response by July 31 from the Office of Drug Safety for at least one of the three proposed tradenames(AVAGE) submitted on July 2, 2002.

PHASE 4 COMMITMENT:

During the labeling discussion, a question arose concerning Allergan's willingness to accept a Phase 4 Commitment to conduct . At this time, Allergan does not intend to complete such a study. Phase 4 commitments are generally intended to answer some as-yet-unresolved clinically important parameter not addressed in the NDA. No such parameter remains outstanding for this clinical supplement.

DESCRIPTION/TRADENAME

We have included in the description a statement that tazarotene is also marketed for the treatment of acne vulgaris and plaque psoriasis as TAZORAC® (tazarotene). This is the format of the verbiage from the PROZAC® (fluoxetine) label regarding its relationship to SERAFEM® (fluoxetine).

ORIGINAL

Following our teleconference, the Project Manager, Kalyani Bhatt, asked Allergan to include in our response the reasons that the naming convention for a TAZORAC®/ relationship would not be analogous to Allergan's Legal/Trademark Department has provided the following statement, which was also sent electronically to the attention of the Project Manager on July 17, 2002:

[

]

- [

]

- TAZORAC® is much different. TAZORAC® could be replaced in formularies by other topical retinoids for acne --Retin-A®, Differin®, and by other non-retinoids for psoriasis--Dovonex®, etc.

Therefore, it is Allergan's intention to move forward with the 3 tradenames previously submitted on July 2, 2002. These were submitted upon the advice of Dr. Bull and at the ODE V Office level after extensive and costly practitioner/pharmacist research and trademark clearance. While " was not submitted nor is agreeable to Allergan, we are hopeful that in the spirit of compromise at least one of the other three non-misleading tradenames will be acceptable to the Division and Office of Drug Safety once the review is complete. "

CLINICAL PHARMACOLOGY:

We have modified this section with the agreed changes and have also added a statement that epidermal edema was also increased in the cited study. We have used the dermatological term "dyspigmentation" to include mottled hyperpigmentation, lentigines and irregular depigmentation.

We have removed the statement that tazarotene cream was associated with . The term "photodamage" was replaced throughout with "fine wrinkling and dyspigmentation (mottled hyperpigmentation, lentigines and irregular depigmentation." The information on the open-label portion of Study A was deleted.

In the tables in this section, the term
" replaced mottled hyperpigmention. We have also added line descriptions following the tables for all three components of mottled hyperpigmentation, lentigines and irregular depigmentation) in place of separate tables for We removed the table.

INDICATIONS AND USAGE:

CONTRAINDICATIONS:

The term "photodamage" was replaced throughout with "fine wrinkling and dyspigmentation (mottled hyperpigmentation, lentigines and irregular depigmentation)."

The number of reported pregnancies was changed from 3 to 10. The number of patients who were found to be on tazarotene was changed from 2 to 9. A statement was added that the patient who elected to terminate the pregnancy terminated for non-medical reasons, unrelated to treatment. The number of patients who delivered healthy babies was changed to 8.

PRECAUTIONS:

was removed from the third sentence.

ADVERSE REACTIONS

Allergan has added a tabular summary of adverse events that characterizes the time to onset and duration of the most frequent events.

There is a reference inserted by FDA that mentions adverse reactions directly related to the "Ocular Unit." As agreed, we have changed this to "eye or eylid"

As before, we are leaving intact the relatively minor changes to the PRECAUTIONS: Information for Patients and the Patient Package Insert that we feel more correctly speaks to the physical aspects of application and use. We will provide a separate copy of the Patient Package Insert for an independent review by the Office of Drug Safety, as you requested.

We ask that the information in this letter and the information previously submitted concerning the tradename and updated safety information be reviewed and maintained in the file of NDA 21-184. During my family leave, should you require further information, please contact Thomas Walton at 714.246.4470 or Peter Kresel at 714.246.6781, Pacific Time.

Sincerely,

Thomas Walton /for

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

TR/tww

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

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APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ALLERGAN	7/26/2002
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
800-347-4500	714.246.4272

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-184

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate	AGN 190168

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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APPLICATION INFORMATION

APPLICATION TYPE (check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

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IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application

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☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
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■ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Response to Labeling Teleconference

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ■ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

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RECEIVED
JUL 29 2002
MEGA/CDER

13 pages redacted from this section of the approval package consisted of draft labeling

ALLERGAN

2525 Dupont Drive P.O Box 19534, Irvine California, USA 92623-9534 Telephone (714) 246-4500 Website: www.allergan.com

July 2, 2002

NDA [illegible]
NC

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540, Room N115
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Rockville, MD 20850

RECEIVED
JUL 03 2002
MEGA/CDER

REF: TRADENAME (tazarotene) Cream, 0.1%
NDA 21-184/S-002
Formal Dispute Resolution Decision

Dear Doctor Wilkin:

In response to the decision letter received from the Director, Office of Drug Evaluation V, dated June 20, 2002, Allergan is submitting to your Division a list of alternative tradenames for your consideration.

The tradenames are listed in order of preference by Allergan and have successfully passed a standard battery of trademark screenings. Further, [redacted] a marketing research company retained by Allergan, completed a prescriber acceptability survey of a representative sample of dermatologists and pharmacists. In this survey, all three of these tested tradenames scored/ranked very favorably in prescriber acceptability (data on file, Allergan, Inc.).

1: [redacted]
2. [redacted]
3. **AVAGE**

We believe, based on the trademark and prescriber research cited above, any of these proposed alternative tradenames lack controversy, are neither confusing nor misleading and will be acceptable to the Division and Office of Drug Safety. As a result, we look forward to successfully working with your Division to quickly reach an agreement on at least one of the proposed tradenames. We are available for any discussion your Division or the Office of Drug Safety wishes to have concerning the proposed alternative tradenames submitted.

We ask that the information in this letter be reviewed and filed to NDA 21-184/S-002. During my family leave, should you require further information, please contact Thomas Walton at 714.246.4470 or Peter Kresel at 714.246.6781, Pacific Time.

Sincerely,

Thomas Walton / for

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

TR/tww

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ALLERGAN	7/2/2002
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
800-347-4500	714.246.4272

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State. ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-184

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Tazarotene (USAN)	Tazorac®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate	AGN 190168

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.05% 0.1%	Topical

RECEIVED
JUL 03 2002
MEGA/CDER

(PROPOSED) INDICATION(S) FOR USE:
Treatment of plaque psoriasis; Treatment of acne vulgaris;

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Tradenames

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ALLERGAN

525 Dupont Drive. P.O. Box 19534 Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website www.allergan.com

SE1-002 / BL

SUPPL NEW CORRESP

June 24, 2002

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540, Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd, Building 2
Rockville, MD 20850

REF: TRADENAME (tazarotene) Cream, 0.1%
NDA 21-184/S-002
Response to Approvable Action Letter received 4/29/02 (partial)

Dear Doctor Wilkin:

Allergan is responding to the Approvable Action Letter received for the above referenced clinical supplement to NDA 21-184. As you know, we previously submitted a response to the Draft Labeling and a teleconference has been scheduled for 2 hours on July 15, 2002 at 10:00 am EDT. As you are aware, there are several areas in which we believe the labeling could be more informative and better reflect the extensive and comprehensive clinical data generated by Allergan. Also, as you know, we have completed the Formal Dispute Resolution Process at the ODE V level concerning the tradename/separate labeling topics (Final Decision dated June 20, 2002. We will promptly forward to your attention, under separate cover, a short list of what we believe will be non-controversial alternative tradenames for your consideration.

The Action Letter also asked Allergan to update our NDAs (20-600 and 21-184) with information from ongoing studies with topical and oral formulations of tazarotene. This information is in response to that request. We were also asked to submit safety data on other tazarotene dosage forms and other indications, labeling from other countries tazarotene has been approved in and distribution figures, also on a worldwide basis.

Please note that there are currently no on-going clinical trails of tazarotene creams or gels

. Data from one other completed topical study is included, Study 190168-045C, a bone safety study completed in psoriasis patients 12 – 17 years old. The final report for this study was previously submitted to your Division (IND[ ]). Therefore, this safety update consists mostly of information on our pharmacovigilance program for topical tazarotene and information on the on-going clinical trials of tazarotene oral formulations for
We have also enclosed, as requested, foreign labeling for recent approvals and information on our global distribution activities.

ORIGINAL

We ask that the information in this letter be reviewed and filed to NDA 21-184/S-002. During my family leave, should you require further information, please contact Thomas Walton at 714.246.4470 or Peter Kresel at 714.246.6781, Pacific Time.

Sincerely,

Thomas Walton for

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

TR/tww

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ALLERGAN	6/24/2002
TELEPHONE NO. *(Include Area Code)* 800-347-4500	FACSIMILE (FAX) Number *(Include Area Code)* 714.246.4272
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State. ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-184

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Tazarotene (USAN)	Tazorac®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate	AGN 190168

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.05% 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Treatment of plaque psoriasis; Treatment of acne vulgaris;

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Response to Approvable Action Letter

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 7 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

RECEIVED
JUN 27 2002
MEGA/CDER

FORM FDA 356h (4/97)

LERGAN

NDA SUPPL AMENDMENT
SE1-002/BL

ipont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website: www.allergan.com

May 14, 2002

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540, Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd, Building 2
Rockville, MD 20850

REF: TRADENAME (tazarotene) Cream, 0.1%
NDA 21-184/S-002
Response to Draft Label received 4/29/02

Dear Doctor Wilkin:

Allergan is responding to the Draft Label received with the Approvable Action Letter for the above referenced clinical supplement to NDA 21-184. We wish to bring this labeling matter to a close as soon as possible, however, there are several areas in which we believe the labeling could be more informative and better reflect the extensive and comprehensive clinical data generated. We have detailed those comments previously in our response of April 25, 2002 to the label received on April 19, 2002.

Please note the following:

TRADENAME/SEPARATE LABELING

Allergan has initiated the Formal Dispute Resolution Process to resolve the tradename and separation of the label for the cosmetic and medical indications that is outside your Division's purview. This process will run in parallel with our labeling discussions related to the scientific and regulatory issues and should not impact our discussions. At this time, we are working from a combined label.
We wish to reiterate our positions on several aspects of the label:

CLINICAL PHARMACOLOGY

Allergan conducted a vehicle-controlled clinical pharmacology study (Study 190168-036C) that investigated the histological effects of patients with photodamaged, but otherwise normal skin in patients for up to six months. Punch biopsies were taken at time 0 and at 24 weeks. The biopsies were examined by an expert pathologist that was not otherwise involved in the study and did not have access to the study blinding code. The biopsies were evaluated primarily for keratinocytic and melanocytic atypia as well as for other dermal and epidermal parameters.

The positive results from this study were not included in the Clinical Pharmacology section. In fact, no data at all were presented in this section for this indication. The End-of-Phase 2 Meeting Minutes (August 20, 1999) state that histologic findings may be reported in mechanism of action under the Clinical Pharmacology section. Therefore, we would expect that the positive pharmacological findings from this study concerning keratinocyte atypia, melanocytic atypia, epidermal thickness and granular cell layers will be reported in this section. We did receive comments from one reviewer who had some disagreement with the methodology. Nevertheless, Allergan stands behind the data generated. The histological slides were forwarded to an outside dermatopathologist for evaluation (in a blinded manner) in December, 2000.

- The dermatopathologist's evaluation was forwarded to Allergan in late December, 2000.
- The statistical analysis plan was signed off January 12, 2001, before randomization was broken.
- The randomization code was broken on January 15, 2001

I have attached a copy of the Histological Parameters Approval Form for your information.

CLINICAL STUDIES

As we described in our previous response, we have modified our original tables for all clinical endpoints to the format suggested to us by the Division in the Draft Labeling received. We have further removed , also as previously stated.

. Therefore, patients and their physicians have the need to know what a reasonable clinical outcome of therapy might be. This table serves that purpose.

Therefore the importance, appropriateness, validity and utility of this information already been demonstrated by FDA.

INDICATIONS AND USAGE

As mentioned in our previous response, the drug product, tazarotene cream 0.1% has been previously approved for the treatment of psoriasis (original NDA) and for the treatment of acne vulgaris (S-001). Following our IND filing and early clinical and nonclinical activities we met with the Division for an End-of-Phase 2 Meeting on August 20, 1999. One of our key questions was if we had chosen appropriate clinical criteria for the indication

We recognize that such a broad indication as ——— ' is not an appropriate indication and the Agency made such a comment in the minutes of the meeting and in other settings. However, the Division made the comment that "the clinical signs can be acceptable as individual indications if the drug is shown to be effective for those particular signs." Further, the Division informed us that we should determine which signs we intend to select as primary, otherwise a statistical penalty may be incurred for multiplicity.

Allergan selected mottled hyperpigmentation and fine wrinkling for the primary endpoints and as secondary parameters we selected elastosis and lentigines. Other parameters were appearance of pore size and irregular depigmentation. Appropriate statistical adjustments were made for multiplicity for all parameters: primary, secondary and other.

Allergan's Phase 3 study designs were constructed and powered to detect these endpoints. We shared our study design with the Division at the End-of-Phase 2 Meeting. The clinical data generated on these endpoints were found to be statistically significant for the primary, secondary and other clinical endpoints *even with the required statistical adjustments for multiplicity.* Therefore our indication should include

differences for each of these signs in both Phase 3 studies.

Our histology study showed positive effects on keratinocytic atypia and melanocytic atypia.

We have modified the statement to correct this inaccuracy. All other statements in this section are acceptable to Allergan.

CLINICAL PHARMACOKINETICS

In reviewing the data, we discovered a needed correction in the safety multiple in this section, ie. bottom of page 8, second line from bottom, with a value of . — The correct value should have been 65. We have revised the —to 65.

In calculating the Area Under the Curve (AUC) ratio between rabbit and human data, the value of 2840 ng.hr/mL represents tazarotenic acid exposure at the lowest observable effective level in the rabbit from a developmental toxicology study (Study 1643-SLS-3202.13, Report PK-94-052). A human AUC value of 44.0 ng.hr/mL was the highest single value observed from the clinical pharmacokinetic study in which tazarotene cream 0.1% was applied to 15% of total body surface area of patients with photodamaged skin (Study 190168-038P). Therefore, the animal/human AUC ratio is calculated to be 65.

WARNINGS/CONTRAINDICATIONS

We have broadly accepted your Division's suggestions and recommendations in these sections.

ADVERSE REACTIONS

There is a reference inserted by FDA that mentions adverse reactions directly related to the "Ocular Unit." Allergan would like to know what tissues and structures are included in this designation, as it does not appear in our COSTART dictionary.

We also made relatively minor changes to the PRECAUTIONS: Information for Patients and the Patient Package Insert that we feel more correctly speaks to the physical aspects of application and use.

In conclusion, Allergan believes that the extensive clinical programs that we have initiated over the past years and the clinical data generated have not been correctly reflected in the Draft Labeling.

We ask that the information in this letter and our response to the Draft Labeling received on April 29, 2002 be reviewed Should you require further information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

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

TR/tww

ALLERGAN

2525 Dupont Drive P.O. Box 19534 Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www.allergan.com

May 13, 2002

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540, Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd, Building 2
Rockville, MD 20850

REF: TRADENAME (tazarotene) Cream, 0.1%
NDA 21-184/S-002
Response to Draft Label received 4/19/02

Dear Doctor Wilkin:

Allergan is requesting a teleconference to discuss the Draft Labeling received with the Approvable Action Letter on April 29, 2002. We have previously requested this teleconference by fax at the suggestion of the Project Manager, Kalyani Bhatt. Ms Bhatt also suggested that the teleconference would run for approximately 2 hours.

We will have Allergan representatives from Regulatory Affairs, Clinical Research, Biostatistics, Scientific Information and Medical Compliance and Clinical Pharmacokinetics present for the meeting. We consider the areas of Clinical Pharmacology, Clinical Studies, Indications and Usage and Information for Patients to be the main areas of focus for the teleconference.

As you may be aware, Allergan has entered into the Dispute Resolution process for the tradename and separation of the label for ——— issues that are the subject of this supplement. Nevertheless, that process will not impact our scientific and regulatory discussions for the label.

We ask that request be granted and a teleconference arranged as quickly as practical. Should you have any questions or require further information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

T. Rumbaugh M.D.

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

TR/tww

NDA SUPPL AMENDMENT SE1-002 BL

LERGAN

Dupont Drive, P.O Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website www.allergan.com

April 25, 2002

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540, Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd, Building 2
Rockville, MD 20850

RECEIVED
APR 26 2002
MEGA/CDER

REF: TRADENAME (tazarotene) Cream, 0.1%
NDA 21-184/S-002
Response to Draft Label received 4/19/02

Dear Doctor Wilkin:

Allergan is responding to the Draft Label received for the above referenced clinical supplement to NDA 21-184. Thank you for meeting with us for a teleconference yesterday. We appreciate your Division's efforts to bring this supplement to an Approval Action Letter. There are, however, several areas in which we believe the labeling could be more informative and better reflect the extensive and comprehensive clinical data generated.

The Mission Statement of the FDA states, in part, *"...regulated products are honestly, accurately and informatively represented."*

The draft label received by Allergan falls short of the Agency's goals for accurate and informative representation of the safety and efficacy of the clinical studies Allergan performed in support of clinical supplement S-002. Further, fair balance requires that the positive effects from our studies be included as well as the negative results obtained using the same criteria.

Please note the following:

TRADENAME/SEPARATE LABELING

Tazarotene cream 0.1% for the indications of acne and psoriasis is known by the tradename of TAZORAC®. For the indication we have provided FDA with ample evidence of other identical drugs with the same formulation/strength, but with different tradenames for different indications and marketed by the same company.

ORIGINAL

At this time, we will accept a combined label. Please note that following approval, Allergan plans to promptly pursue the separation of the label for the S-002 indication from the acne and psoriasis label and also pursue activities that provide for the [redacted] tradename for the separated label. This information and our ultimate goal for the label and tradename have been previously communicated to your Division, both orally and in writing with the data supporting our position:

We believe there is ample regulatory and legal precedent to support our position. We believe there poses no sufficient safety reason not to approve a separate label/tradename and in fact doing so will assist physicians, patients, and managed care in distinguishing the products and indications, thereby preventing any confusion.

Furthermore, we believe the Agency's prior precedents in allowing different tradenames and the basic commercial free speech, First Amendment issues at stake justify supporting our position that a separate tradename and label are necessary. And to do less could be interpeted as being an arbitrary Agency action.

CLINICAL PHARMACOLOGY

Allergan conducted a vehicle-controlled clinical pharmacology study (Study 190168-036C) that investigated the histological effects of patients with photodamaged, but otherwise normal skin in patients for up to six months. Punch biopsies were taken at time 0 and at 24 weeks. The biopsies were examined by an expert pathologist that was not otherwise involved in the study and did not have access to the study blinding code. The biopsies were evaluated primarily for keratinocytic and melanocytic atypia as well as for other dermal and epidermal parameters.

The positive results from this study were not included in the Clinical Pharmacology section. In fact, no data at all were presented in this section for this indication. The End-of-Phase 2 Meeting Minutes (August 20, 1999) state that histologic findings may be reported in mechanism of action under the Clinical Pharmacology section. Therefore, we would expect that the positive pharmacological findings from this study concerning keratinocyte atypia, melanocytic atypia, epidermal thickness and granular cell layers will be reported in this section. We have reinstated a more concise version to this section than originally proposed by Allergan.

CLINICAL STUDIES

We have modified our original tables for all clinical endpoints to the format suggested to us by the Division in the Draft Labeling received. We have further removed the tables for

, also as suggested by the Division.

A product intended for no other purpose than the enhancement of one's physical appearance and psychological well-being. Therefore, patients and their physicians have the need to know what a reasonable clinical outcome of therapy might be. This table serves that purpose.

Therefore the importance, appropriateness and utility of this information for a cosmetic indication have already been demonstrated.

INDICATIONS AND USAGE

The drug product, tazarotene cream 0.1% has been previously approved for the treatment of psoriasis (original NDA) and for the treatment of acne vulgaris (S-001). Following our IND filing and early clinical and nonclinical activities we met with the Division for an End-of-Phase 2 Meeting on August 20, 1999. One of our key questions was if we had chosen appropriate clinical criteria for the indication

We recognize that such a broad indication as " " is not an appropriate indication and the Agency made such a comment in the minutes of the meeting and in other settings. However, the Division made the comment that "the clinical signs can be acceptable as individual indications if the drug is shown to be effective for those particular signs." Further, the Division informed us that we should determine which signs we intend to select as primary, otherwise a statistical penalty may be incurred for multiplicity.

Allergan selected mottled hyperpigmentation and fine wrinkling for the primary endpoints and as secondary parameters we selected elastosis and lentigines. Other parameters were appearance of pore size and irregular depigmentation. Appropriate statistical adjustments were made for multiplicity for all parameters: primary, secondary and other.

Allergan's Phase 3 study designs were constructed and powered to detect these endpoints. We shared our study design with the Division at the End-of-Phase 2 Meeting. The clinical data generated on these endpoints were found to be statistically significant for the primary, secondary and other clinical endpoints *even with the required statistical adjustments for multiplicity.* Therefore our indication should include fine wrinkling, mottled hyperpigmentation, lentigenes, since there were significant differences for each of these signs in both Phase 3 studies

Our histology study showed positive effects on keratinocytic atypia and melanocytic atypia.

We have modified the statement to correct this inaccuracy. All other statements in this section are acceptable to Allergan.

CLINICAL PHARMACOKINETICS

In reviewing the data, we discovered a needed correction in the safety multiple in this section, ie. bottom of page 8, second line from bottom, with a value of ~ The correct value should have been 65. We have revised the ~ to 65.

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ADVERSE REACTIONS

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We also made relatively minor changes to the PRECAUTIONS: Information for Patients and the Patient Package Insert that we feel more correctly speaks to the physical aspects of application and use.

In conclusion, Allergan believes that the extensive clinical programs that we have initiated over the past years and the clinical data generated have not been correctly reflected in the Draft Labeling.

We ask that the information in this letter and our response to the Draft Labeling received on April 19, 2002 be reviewed Should you require further information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

T. Rumbaugh M.D.

Trudy A. Rumbaugh, MD
Senior Director,
[redacted] Regulatory Affairs, Retinoids

TR/tww

22 pages redacted from this section of the approval package consisted of draft labeling

ALLERGAN

2525 Dupont Drive, P.O Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website www.allergan.com

April 15, 2002

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

REF: Tazarotene Cream, 0.1%
NDA 21-184/S-002
Proposed Tradename for Tazarotene Cream 0.1%

Dear Doctor Wilkin:

Following our electronic mail exchange and your teleconference with Peter Kresel on April 12, 2002, Allergan is supplying your Division with additional information concerning our application for a tradename and product labeling distinct from that approved for TAZORAC® (tazarotene) Cream 0.05%, 0.1%.

As you know, TAZORAC® (tazarotene) Cream 0.05%, 0.1% is currently approved for the treatment of acne vulgaris (0.1%) and plaque psoriasis (0.05%, 0.1%). S-002 seeks the approval for the use of Tazarotene Cream 0.1%

Our proposal is for Tazarotene Cream, 0.1% for this indication to be known as:

[redacted](tazarotene) Cream, 0.1%.

Also as you know, Allergan included in the filing of S-002 (as Attachment 3 to the Cover Letter) a rationale for the use of labeling and a tradename separate and distinct from TAZORAC® Cream. Today, new information has become available that supports our earlier tradename rationale and builds further on our rationale for differentiation.

++++++++++++++++++++++++++

Allergan, Inc. markets a broad spectra of prescription and OTC health care products intended to treat diseases and conditions across several disparate therapeutic areas. In the United States, Allergan, Inc.'s regulated products are reviewed by several FDA Centers: CDER (pharmaceuticals), CDRH (intraocular lenses, contact lens care) and CBER (BOTOX® botulinum toxin Type A).

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

For your convenience, the following are attached:

-
-

We ask that this additional information be reviewed and filed to NDA 21-184/S-002 and that our proposed tradename [redacted] be approved for Tazarotene Cream 0.1% for the indication. Should you have any questions or require further information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

T. Rumbaugh M.D.

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

TR/tww

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ALLERGAN	4/15/2002
TELEPHONE NO. *(Include Area Code)* 800-347-4500	FACSIMILE (FAX) Number *(Include Area Code)* 714.246.4272

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State. ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-184

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Tazarotene (USAN)	Tazorac®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate	AGN 190168

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.05% 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Treatment of plaque psoriasis; Treatment of acne vulgaris;

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Trade name Data

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, [illegible]s, IDEs, BMFs, and DMFs referenced in the current application)

22 pages redacted from this section of the approval package consisted of draft labeling

ALLERGAN

2525 Dupont Drive, P.O Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

February 19, 2002

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

REF: Tazarotene Cream, 0.1%
NDA 21-184/S-002
Updated Tradename for Tazarotene Cream 0.1%

Dear Doctor Wilkin:

Allergan is supplying your Division with our application for an updated tradename and product labeling distinct from that approved for TAZORAC® (tazarotene) Cream 0.05%, 0.1%.

We had previously applied to use the following tradename:

[redacted](tazarotene) Cream, 0.1%.

Actually, it should have been submitted as:

[redacted](tazarotene) Cream, 0.1%.

Note the only difference is an accent mark over the

We have carefully researched this tradename for any trademark infringements: none exists. Also, Allergan believes [redacted] does not conflict with any current tradename or generic name such that a safety concern would be elicited.

As stated before, the TAZORAC® tradename will continue to be used for tazarotene gels and creams for the indications of the topical treatment of acne vulgaris and plaque psoriasis.

We ask that this additional information be reviewed and filed to NDA 21-184/S-002 and that our proposed tradename, [redacted] be approved for Tazarotene Cream 0.1% for the indication. Should you have any questions or require further information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

T. Rumbaugh M.D.

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

TR/tww

:RGAN

SE1-002 | NC

t Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone (714) 246-4500 Website www.allergan.com

Jan · 21, 2002

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Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

REF: Tazarotene Cream, 0.1%
NDA 21-184/S-002
Proposed Tradename for Tazarotene Cream 0.1%

Dear Doctor Wilkin:

Allergan is supplying your Division with our application for a tradename and product labeling distinct from that approved for TAZORAC® (tazarotene) Cream 0.05%, 0.1%.

As · know, TAZORAC® (tazarotene) Cream 0.05%, 0.1% is currently approved for the tr nt of acne vulgaris (0.1%) and plaque psoriasis (0.05%, 0.1%). S-002 seeks the approval for the use of Tazarotene Cream 0.1% in the It is our intention that for this indication Tazarotene Cream, 0.1% will be known as:

(tazarotene) Cream, 0.1%.

We have carefully researched this tradename for any trademark infringements: none exists. Also, Allergan believes does not conflict with any current tradename or generic name such that a safety concern would be elicited.

Allergan included in the filing of S-002 (as Attachment 3 to the Cover Letter) a rationale for the use of labeling and a tradename separate and distinct from TAZORAC® Cream. For your convenience, I have enclosed this Attachment again, as all points in it remain relevant.

The TAZORAC® tradename will continue to be used for tazarotene gels and creams for the indications of the topical treatment of acne vulgaris and plaque psoriasis.

ORIGINAL

We ask that this additional information be reviewed and filed to NDA 21-184/S-002 and that our proposed tradename, [redacted] be approved for Tazarotene Cream 0.1% for the indication. Should you have any questions or require further information, please contact me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

T. Rumbaugh M.D.

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

TR/tww

ALLERGAN

2525 Dupont Drive, P.O Box 19534, Irvine, California, USA 92623-9534 Telephone. (714) 246-4500 Website. www.allergan.com

October 30, 2001

Jonathan Wilkin, MD
Director
Division of Dermatological and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd; Building 2
Rockville, MD 20850

REF: Tazarotene Cream Formulation, 0.1%
NDA 21-184/S-002
120-Day Safety Update

Dear Doctor Wilkin:

Allergan is amending the above-referenced supplement with the 120-Day Safety Update in accordance with **21 §CFR 314.50(d)(5)(vi)(b).**

This Safety Update consists of the following:

- Final Clinical Study Report (CSR) for Study 190168-033C
- Updated Product Labeling
- Updated Integrated Summary of Safety
- Case Report Tabulations
- Case Report Forms (CRFs) for subjects discontinuing due to adverse events.

We ask that this update be reviewed and filed to NDA 21-184/S-002. Should you have any questions or require further information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

T. Rumbaugh M.D.

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

TR/tww

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

June 28, 2001

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

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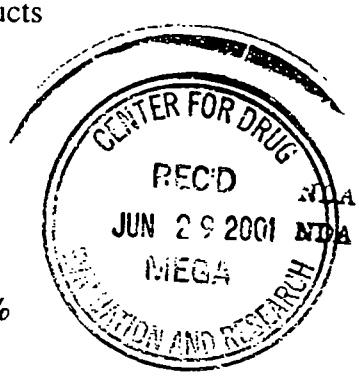

NDA NO. 21-184 REF. NO. 002
NDA SUPPL FOR SE1

REF: Tradename® (tazarotene) Cream, 0.1%
NDA 21-184/ User Fee Number 4148
Clinical Efficacy Supplement:

Dear Doctor Wilkin:

Allergan is supplementing the above-referenced NDA with a clinical efficacy supplement for the use of Tradename® (tazarotene) Cream, 0.1% in the once-daily

As you know, the same formulation, known as TAZORAC® (tazarotene) Cream, 0.1% is currently approved for the treatment of plaque psoriasis. A 0.05% concentration of TAZORAC® Cream is also approved for the treatment of psoriasis. A clinical supplement (S-001) for TAZORAC® Cream 0.1% is currently under review in your Division for the treatment of acne vulgaris.

This supplement is being filed according to the provisions of **21 CFR §314.70(b)(3)**, **21 CFR §314.71(a)-(c)**, the Prescription Drug User Fee Act, and the agreements and commitments made between Allergan and your Division at the PreNDA Meeting of February 21, 2001. We have included a copy of the meeting minutes for your reference in the application.

In addition to the nonclinical safety and clinical safety and efficacy data that support the new indication and labeling, we have, as agreed in the PreNDA Meeting, included an updated Environmental Assessment and a statement that there have been no changes to the formulation of the tazarotene API nor to the finished dosage forms which this applications references.

Other than the previously mentioned clinical supplement, there are two open regulatory issues on-going with NDA 21-184. To address these issues, Allergan currently has two, in-progress clinical studies that your Division had requested Allergan perform. One study is a bone safety study in psoriasis patients 12-17 years of age and the other study seeks to enroll women who inadvertently become pregnant while on TAZORAC® Gel or Cream treatments for psoriasis.

ORIGINAL

A number of clinical studies with tazarotene cream support the dose, safety and efficacy for the indication. One clinical pharmacokinetics study, one histology safety study, one Phase 2 dose-ranging study and two, Phase 3 clinical studies support the indication. Both Phase 3 studies were multi-center, double-blind, randomized, vehicle-controlled studies that evaluated the safety and efficacy of tazarotene cream, 0.1% for 24-weeks in the once-daily treatment —
— One of the Phase 3 studies is continuing for an additional 24 weeks as an open-label safety study. As agreed upon with your Division, this data will be reported in the 120-Day Safety Update.

The results of both studies (double-blind portions) indicated that Tradename® (tazarotene) Cream, 0.1% was safe and significantly more effective than vehicle cream in the reduction of fine wrinkling and mottled hyperpigmentation, the primary efficacy variables. The results also indicated a significant effect over vehicle in the reduction of lentigenes. —
—

This supplement consists of both Archival and Review copies. All of this supplement is presented in electronic format on aCD ROM in accordance with the agreements from the PreNDA Meeting and **21 CFR § 11** (except for those forms, certifications and commitments requiring a "wet" signature presented as original documents). See *Attachment 1* to this cover letter that describes in greater detail the contents of the electronic portion of the supplement. Also included is a verification that Allergan has performed a scan of the submission for virus protection. *Attachment 2* details the FDA locations receiving the Review, Archival and Field copies.

A Field Copy of Sections 1, 2, 3 and 4 has been printed from the electronic file and forwarded to FDA's Dallas District Office, as the Drug Product is manufactured at the Allergan Waco, Texas facility. The Field Copy is paper, generated from the identical database from which the Review and Archival sections (electronic) were created. At this time, all Allergan facilities utilized in the development, validation, manufacturing and quality assurance of tazarotene cream, 0.1% (Irvine, California; Waco, Texas; Westport, Ireland) are prepared for pre-approval inspections.

Attachment 3 details Allergan's rational for a separate and distinct trade name to be utilized for tazarotene cream 0.1% that is labeled for the —
—

We ask that this Clinical Efficacy Supplement be filed to NDA 21-184. Should you have any questions or require additional information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

T. Rumbaugh M.D.

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

ATTACHMENT 1

Disposition of the Electronic Submission:

As agreed in the PreNDA Meeting (February 21, 2001), both the Archival and Review Copies are being submitted totally in electronic format. Every effort has been made to comply with the Guidance for Industry: Providing Regulatory Submissions in Electronic Format—NDAs, IT3, January, 1999.

A complete copy of the efficacy supplement is contained on one CD ROM, comprised of approximately 600 megabytes. Two copies are being delivered to FDA. One CD for archive is being delivered to the Center for Drug Evaluation and Research's Central Document Room at Wilkins Avenue, Rockville, MD. The Archival CD will also be accompanied by hard (paper) copies of "wet" signature documents: Cover Letter, Form FDA 356h, Financial Disclosure, Debarment Certification and Field Copy Certification. As agreed in the PreNDA Meeting, the other CD is being delivered directly to the review division (Division of Dermatologic and Dental Drug Products).

Section 11

The data sets from the two, Phase 3 pivotal studies, Studies 190168-033C and 190168-034C, are being provided as SAS transport files along with their data definitions.

Section 12

Case Report Forms are organized by study and then by study site (investigator) and bookmarked.

Allergan verifies that the electronic format submitted for this clinical efficacy supplement is virus free. Norton® Anti-virus version 5.0 software was used to check the files for viruses.

ATTACHMENT 2

Disposition of the Paper and Electronic Submissions:

FDA Locations			
	Rockville		Dallas*
NDA Section	Review	Archival	Field
1	electronic	paper/electronic	paper
2	electronic	electronic	paper
3	electronic	electronic	paper
4	electronic	electronic	paper
5	electronic	electronic	N/A
6	electronic	electronic	N/A
7	N/A	N/A	N/A
8	electronic	electronic	N/A
9	N/A	N/A	N/A
10	electronic	electronic	N/A
11	electronic	electronic	N/A
12	electronic	electronic	N/A
13	N/A	N/A	N/A
14	N/A	N/A	N/A
15	N/A	N/A	N/A
16	electronic	paper/electronic	N/A
17	electronic	paper/electronic	paper
18	electronic	electronic	N/A

*Dallas is the District Office in which Allergan, Inc., Waco, Texas is located, the manufacturing and release location for Tazarotene Cream.

ATTACHMENT 3

Rationale for a separate trade name for tazarotene cream 0.1% for

PATIENT SAFETY:

TAZORAC® creams and gels 0.1% and 0.05% are currently indicated for the treatment of plaque psoriasis and TAZORAC® gel 0.1% is also indicated for the treatment of acne vulgaris. TAZORAC® cream 0.1% for the treatment of acne vulgaris is also the subject of a clinical supplement which is currently under review at the agency. The experience with TAZORAC® creams and gels has indicated that tazarotene is a very safe drug when used under a physician's care and according to the approved labeling. It is Allergan's intention that tazarotene containing-formulations continue to be used safely and in exact accordance with their approved labeling.

This current efficacy supplement seeks approval for the use of tazarotene cream 0.1% for the

There is strong evidence that overexposure to the sun is related to the development of certain types of skin cancer and pre-cancerous conditions such as actinic keratoses. Allergan recognizes that the such as mottled hyperpigmentation, fine wrinkling, lentigines, associated with the use of tazarotene cream 0.1% has more direct relevance to claims. Allergan offers no labeling claim in this supplement that direct medical benefits are achieved. We do provide ample evidence to show that tazarotene cream 0.1% is both safe and effective for the

Allergan believes that there are some causes for concern should the claims appear together with the claims on labeling for TAZORAC®. Allergan's main concern is that patients may overuse or share their medication inappropriately. For instance, patients who might be undergoing treatment with tazarotene gel or cream for the treatment of psoriasis or acne, may consider but not necessarily under the guidance of a physician. In this day of the mass media's focus on health and with publications such as the PDR available on the Internet, today's consumers/patients are remarkably well-informed. It is expected that patients would have knowledge of TAZORAC®' claims, irrespective of whether they received the full prescribing information with their prescription or not. Although topical retinoids are very safe when used according to their labeling, they remain potent medications that should not be used indiscriminately.

. Allergan feels, as a health care company, that a physician is the only person who should be diagnosing the condition and

recommending treatment, especially when an Rx product is involved. The situation whereby claims share the same label on a product is an invitation to potential problems of misuse or overuse.

REIMBURSEMENT

Most Rx pharmaceutical products in the United States are "on formulary" and reimbursed by third-party payers such as employers, government agencies, insurance companies, HMOs and preferred provider networks, among others. This reimbursement does not normally extend to products intended to treat conditions, except in certain specialized instances or for disfiguring conditions.

Currently, tazarotene creams and gels are, for the most part, reimbursed under the trade name of TAZORAC® for the treatments of acne vulgaris and plaque psoriasis, as is customary for those disease-state conditions. therefore, is not likely to be reimbursed by a third-party payer. It is also likely that many, if not most or all formularies might remove TAZORAC® from its reimbursable status should condition be approved under the same trade name. This scenario developed with Retin-A® (tretinoin) when reports were first circulated in the scientific literature concerning the possible beneficial effects of topical tretinoin in the treatment of "photodamaged" skin. As a result of that information, it became very difficult to prescribe Retin-A® for any patient over the ages of 25-30 years, regardless of their medical condition, due to the reluctance of third party payers to reimburse for cosmetic conditions. We would expect much the same situation with tazarotene cream 0.1% and even with other formulations and strengths of tazarotene, should we not be allowed a separate and distinct trade name. This would in effect deprive patients with psoriasis or acne access to an important medication with distinct and unique effects.

Therefore, in order for TAZORAC® to remain a commercially viable product, to continue to be able to compete and to provide its unique therapeutic advantages in the treatment of psoriasis and acne, we believe that it is in the best interest of all (patients, physicians, FDA, third-party payers as well as Allergan) to allow a separate trade name and label for the indication of

PRECEDENTS:

Although most products that have a different tradename while containing the same dose or concentration of active drug substance have a slightly different vehicle (minor change in one or more of the excipients for example), there are several examples where identical products have been marketed under different brand names. Photoplex® Broad Spectrum Sunscreen Lotion, which was approved by FDA (NDA 19-459) was also marketed as Filteray® Sunscreen. Erygel® (erythromycin) 2% Gel (NDA 50-617) was also marketed as A/T/S® (erythromycin) 2% Gel.

Furthermore, Allergan does not view the argument that a product must have a different (albeit only slightly) formulation in order to be assigned a distinct and separate trade name as inherently having a logical or rational basis. Each drug product, regardless of name is required to stand on its own merit and to have data supporting its safety and efficacy for a particular indication. This is certainly true for tazarotene cream 0.1%. Additionally, the overwhelming majority of patients and physicians are unaware of subtle distinctions around rules that have perhaps evolved around product naming conventions and so having a distinct product name is unlikely to cause confusion for these groups. Allergan believes it is clearly of benefit to have a different trade name for a product like tazarotene cream, 0.1%, currently indicated for the treatment of psoriasis (and under review for acne),when it also has beneficial effects in a very disparate condition such as that represented by the

Therefore, Allergan submits that a separate trade name and separate label for the indication for tazarotene cream 0.1% would seem most appropriate on grounds of patient safety and the need to avoid more general product-availability problems that might develop due to third-party reimbursement issues. Additionally, it might be pointed out that there are several precedents for identical products having distinct trade names and a dearth of specific rational arguments against this particular concept.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Allergan, Inc.	6/28/2001
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
800-347-4500	714.246.4272

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State. ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-184

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Tazarotene (USAN)	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate	AGN 190168

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE:
C ... J

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☒ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Clinical Efficacy Supplement

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

RECEIVED
JUN 2 9 2001
CDR/CDER

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Rockville MD 20857

NDA 21-184/S-002

PRIOR APPROVAL SUPPLEMENT

Allergan, Inc.
Attention: Trudy A. Rumbaugh, MD
Director, Global Regulatory Affairs
2525 Dupont Drive
PO Box 19534
Irvine, CA 92623-9534

Dear Dr. Rumbaugh:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tazarotene Cream, 0.1%

NDA Number: 21-184

Supplement Number: S-002

Review Priority Classification: Standard (S)

Date of Supplement: June 28, 2001

Date of Receipt: June 29, 2001

This supplement provides for the indication, ———

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 28, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 29, 2001 and the secondary user fee goal date will be June 29, 2002.

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). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drug Products, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

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

Sincerely,

/S/

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research