CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-184/S-001

Administrative Documents

1.4 PATENT INFORMATION/CERTIFICATION

The following patent information has been recorded for the Active Pharmaceutical Ingredient, tazarotene and the finished dosage form for the approved gel formulation, Tazorac® (tazarotene topical gel) 0.05%, 0.1%.

Copies of the documentation is attached.

Reference	Date	Subject
Patent Number 5,032,341	June 11, 1991	Compounds having a di-substituted acetylene moiety and retinoic acid-like activity
Patent Number 5,089,509	February 18, 1992	Di-substituted acetylenes bearing heteroaromatic and heterobicyclic groups having retinoid-like activity
Federal Register, Vol. 64, No. 97,	May 20, 1999	Determination of regulatory review period for purposes of patent extension; Tazorac®

I certify that the patent and patent extension information in the New Drug Application is, to the best of my knowledge and belief, factually true and correct.

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

Sept 21, 1999
Date

United States Patent [19]

Chandraratna

[11] Patent Number: 5,023,341

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

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

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

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

[21] Appl. No.: 409,477

[22] Filed: Sep. 19, 1989

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

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

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

[56] References Cited

U.S. PATENT DOCUMENTS

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

FOREIGN PATENT DOCUMENTS

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

OTHER PUBLICATIONS

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

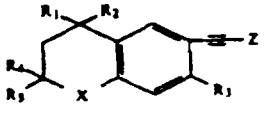
A Convenient Synthesis of Ethynylarenes and Diethynylarenes, by S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* 1980, pp. 627-630.

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

Primary Examiner—Frederick E. Waddell
Assistant Examiner—Raymond Covington
Attorney, Agent, or Firm—Gabor L. Szekeres; Martin A. Voet; Robert J. Baran

[57] ABSTRACT

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



9 Claims, No Drawings

EXCLUSIVITY SUMMARY for NDA # 21-184 SE1-001

Trade Name Tazorac® Generic Name: (tazaortene) topical cream 0.1%
Applicant Name ALLERGAN
Approval Date October 11, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_ / NO /__X /

   b) Is it an effectiveness supplement? YES /_X__/ NO /__/

      If yes, what type(SE1, SE2, etc.)? SE1-001

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

   d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years of exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-600 Tazarotene gel 0.5%, 0.1%

NDA # 21-184 Tazorac (tazarotene)topical cream 0.5% & 0.1%

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

#1 #2 029C 031C

Investigation #1, Study # 190168-029C;190168-031C;190168-035C,190168-41C;190168-025C

Investigation #2, Study # 190168-022;190168-030

Investigation #3, Study # 190168-018P

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /__X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X___/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # 190168-029C

Investigation #__, Study # 190168-031C

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study. Yes

the study. Yes

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [_____] YES /_X__/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /_X__/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

_____ 10-08-01

Signature of Preparer Date

Title: Kalyani Bhatt

/S/ 10/10/01

Signature of ~~Office of~~ Division Director Date

cc:
Archival NDA 21-184
HFD- 540/Division File
HFD- 540 /-+

Bhatt
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

1.5 REQUEST FOR WAIVER OF PEDIATRIC STUDIES

Allergan, Inc. is requesting a partial waiver of pediatric study requirements for neonates, infants and children as:

TAZORAC® (tazarotene) Cream 0.1% does not represent a substantial therapeutic benefit over existing anti-acne treatments, and TAZORAC® (tazarotene) Cream 0.1% would not likely be used in a substantial number of these patients.

Further, acne vulgaris is not prevalent in this prepubescent patient population (birth-11 years).

/S/ 10/10/01

Edit Pediatric Information for Submission N021184 - SE1/001

Note: This page only needs to be completed for approvals.

All blue underlined words on this page are hyperlinks
Glosssary
General Directions

Indication

Acne Vulgaris

Adequacy of Proposed label: Adequate for SOME pediatric age groups

Formulation Status: NO NEW FORMULATION is needed

Decision Date: 2001-10-10 00:00:0

Comments & Recommendations (please date):

The pediatric program has included studying pediatric patients above the age of 12 in Phase 3 clincial trials. Since acne is very rare before puberty, teh program is acceptable. A partial waiver has been requested by th applicant for studies in neonates, infants and children. This waiver may be granted.

Related Applications:

Enter Pediatric Ranges Below

Application Range	Current Status/Due Date	Final Status/Date *(for deferred only)*
Min. 12 Max. Adult ☐ kg ☐ mo. ☐ yr. ☐ kg ☐ mo. ☐ yr.	Status: Waived Due Date: 2001-10-11 0	Status: Waived Action Date: 2001-10-11 0

Reasons for Waivers and Deferrals/Comments:

See Clinical review. Partial waiver granted for neonates, infants and children.

[redacted]

10/10/01

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached listing	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

[(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Eric Brandt	Corporate Vice President and Chief Financial Officer
FIRM/ORGANIZATION: Allergan, Inc.	
SIGNATURE	DATE: 11/21/00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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ALLERGAN

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50 years GROWTH & INNOVATION

1.3 DEBARMENT CERTIFICATION

Under Section 306(k) of the United States Food, Drug and Cosmetic Act, Allergan, Inc. has made a diligent effort to ensure that no individual, corporation, partnership or association debarred under Sections 306(a)-(b) of the Act, as referenced above, has provided any services in connection with this application.

Peter A. Kresel, MS, MBA

Senior Vice President, Global Regulatory Affairs

Allergan, Inc.

Nov 27, 2000

Date

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