

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-275

ADMINISTRATIVE DOCUMENTS

1.4 PATENT INFORMATION AND CERTIFICATION

The following patents are currently in effect for bimatoprost containing ophthalmic preparations. A copy of the patent is enclosed.

Patent Number	Patent Title	Expiration Date
U.S. Patent No. 5,688,819	Cyclopentane, heptanoic acid, 2-cycloalkyl or arylalkyl derivatives as therapeutic agents	September 21, 2012

I, the undersigned, hereby declare that Patent No 5,688,819 covers the formulation, composition, and/or method of use of LUMIGAN™ (bimatoprost ophthalmic solution) 0.03%. This product is the subject of this application for which approval is being sought.



Peter Kresel, MS, MBA
Sr. Vice President, Global Regulatory Affairs
Allergan, Inc.



(Date)

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

5 years

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 /___/ NO /_X_/

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

NDA # _____
NDA # _____
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 /___/

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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /___/ 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 /___/ 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 /___/ 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 /___/

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 /___/

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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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 /___/
Investigation #2 YES /___/ NO /___/
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 # _____
Investigation #__, Study # _____
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.

(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 /___/	NO /___/ Explain: _____
	!	_____
	!	_____
Investigation #2	:	
IND # _____	YES /___/	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 /___/

If yes, explain: _____

/S/
 Signature of Preparer
 Title: MEDICAL OFFICER

2/28/01
 Date

/S/
 Signature of ~~Office of~~ Division Director
Deputy

3/5/01
 Date

1.5 CERTIFICATION FOR MARKETING EXCLUSIVITY

Allergan, Inc. (the applicant) is submitting information in support of a request for five-year exclusivity per Sections 505(c)(3)(D) and 505(j)(4)(D) of the Federal Food, Drug and Cosmetic Act for NDA 21-275, LUMIGAN™ (bimatoprost ophthalmic solution) 0.03%.

The results of the following two controlled clinical studies demonstrated that LUMIGAN™ ophthalmic solution is safe and efficacious for the treatment of the signs and symptoms of ocular hypertension or open-angle glaucoma. In the applicant's opinion these studies are essential to the approval of the new drug application for LUMIGAN™ ophthalmic solution. The applicant was the sponsor of [REDACTED] under which these clinical studies were conducted.

192024-008-00

A Multi-Center, Double-Masked, Randomized, Parallel, Three-Month Study (with Treatment Extended to One Year) of the Safety and Efficacy of AGN 192024 0.03% Ophthalmic Solution, Administered Once-Daily or Twice-Daily Compared with Timolol 0.5% Ophthalmic Solution Administered Twice-Daily, in Subjects with Glaucoma or Ocular Hypertension.

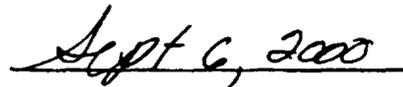
192024-009-00

A Multi-Center, Double-Masked, Randomized, Parallel, Three-Month Study (with Treatment Extended to One Year) of the Safety and Efficacy of AGN 192024 0.03% Ophthalmic Solution, Administered Once-Daily or Twice-Daily Compared with Timolol 0.5% Ophthalmic Solution Administered Twice-Daily, in Subjects with Glaucoma or Ocular Hypertension.

Allergan, Inc. hereby certifies that to the best of our knowledge, the clinical investigations listed herein have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application or supplement. Furthermore, no other drug product containing all of the same ingredients with the same conditions of approval has been previously approved for human use. The scientific literature has been thoroughly searched and in the applicant's opinion there are no published studies or publicly available reports for clinical investigations (other than those sponsored by the applicant) to support the approval of the new drug application for LUMIGAN™ ophthalmic solution. The applicant is not aware of any approvals of the product for human use.



Peter Kresel, MS, MBA
Sr. Vice President, Global Regulatory Affairs
Allergan, Inc.



(Date)

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ON ORIGINAL**

FDA Links Tracking Link Calendars Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

[View as Word Document](#)

NDA Number: 021275 **Trade Name:** LUMIGAN (BIMATOPROST) 0.03% OPHTHALMIC
Supplement Number: 000 **Generic Name:** BIMATOPROST
Supplement Type: N **Dosage Form:**
Regulatory Action: OP **COMIS Indication:** REDUCTION OF ELEVATED INTRAOCULAR PRESSURE IN PATIENTS WITH GLAUCOMA OR OCULAR HYPERTENTION
Action Date: 9/18/00

Indication # 1 Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurement over time) to another intraocular pressure lowering medication.

Label Adequacy: Does Not Apply

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): The sponsor proposed studies in the pediatric population to gain exclusivity. Since the adverse events found with this medication make it inappropriate for use in the pediatric population, the agency has denied this proposal.

Ranges for This Indication

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
0 years	18 years	Waived	

Comments: Adverse events found with this medication make it inappropriate for use in the pediatric population.

This page was last edited on 3/6/01

Signature

TS/

Date

March 6, 2001

**APPEARS THIS WAY
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1.6 DEBARMENT CERTIFICATION

Allergan, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Peter Kresel

Sept 6, 2000

Peter Kresel, MS, MBA
Sr. Vice President, Global Regulatory Affairs

(Date)

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	Form Approved: OMB No. 0910-0398 Expiration Date: 3/31/02
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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 Investigator		

- (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 ERIC BRANDT	TITLE CHIEF FINANCIAL OFFICER
FIRM/ORGANIZATION ALLERGAN, INC.	
SIGNATURE 	DATE 7/21/00

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

FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTGATORS

The following is the list investigators who require certifying the absence of financial interests and arrangements. These investigators participated in the 192024-008 or 192024-009 clinical studies of AGN 192024. The sponsor has not entered into any financial arrangement with these investigators 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). 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. No listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Study Numbers	Principal Investigator Name (Number) and Address	Sub-Investigator(s)
192024-009	Mark Abelson, MD (1584) Ophthalmic Research Associates 863 Turnpike Street, Suite 224 North Andover, MA 01845 USA	Terry Chin, OD Jack V. Greiner, OD, DO, PhD Kathleen Krezner, OD, PhD Charles Leahy, OD N. Jerome Crampton, MD John Pietriantonio, OD Timothy Jordan, OD Nabeel Jarudi, MD
192024-009	George Baerveldt, MD (0359) Edward Rockwood, MD Cleveland Clinic Foundation Department of Ophthalmology 9500 Euclid Avenue, A-31 Cleveland, OH 44195 USA	Edward Rockwood, MD
192024-008	Allen Beck, MD (2999) Emory University Eye Center 1365 B Clifton Road NE Atlanta, GA 30322 USA	Anastasios Costarides, MD Reay Brown, MD Lynn Harmann, MD
192024-009	Steven Best, MD (2671) Saint Marks Eye Centre 8 Saint Marks Road, Remuera Auckland 1005 New Zealand	Justin Mora, MD
192024-009	James Branch, MD (3225) 3001 Maplewood Avenue Winston, NC 27103 USA	None
192024-009	James Brandt, MD (2846) Lawrence Ellison Ambulatory Care Center, Ophthalmology Clinic 4860 Y Street, Suite 2400 Sacramento, CA 95817 USA	Esther Kim, MD
192024-009	John Brennan, MD (3219) 425 North Highland Sherman, TX 75092 USA	Armin Vishteh, MD
192024-009	Anne Brooks, MD (2008) Royal Victorian Eye & Ear Hospital 126 Victoria Parade East Melbourne, Victoria 3002 Australia	William Gillies, MD
192024-009	Salim Butrus, MD (3209) 650 Pennsylvania Avenue SE Suite 270 Washington, DC 20003 USA	Leonard M. Friedman, MD David F. Plotsky, MD
192024-009	Leonard Cacioppo, MD (2957) Hernando Eye Institute 14543 Cortez Boulevard Brooksville, FL 34613 USA	James Jachimowicz, MD

Study Numbers	Principal Investigator Name (Number) and Address	Sub-Investigator(s)
192024-008	Louis Cantor, MD (2117) Department of Ophthalmology Indiana University Medical Center 702 Rotary Circle Indianapolis, IN 46202 USA	Darrell WuDunn, MD, PhD Alan Burnstein, MD Charles D. Finley, MD
192024-008	George A. Cioffi, MD (2855) 1040 Northwest 22 nd Avenue, Suite 200 Portland, OR 97210 USA	Elizabeth Donohue, MD
192024-008	John Cohen, MD (1176) Cincinnati Eye Institute 10494 Montgomery Road Cincinnati, OH 45242 USA	Michael R. Parker, OD Jessica Hildenbrand, OD
192024-008	David Cooke, MD (2232) Great Lakes Eye Care 2848 Niles Road St. Joseph, MI 49085 USA	Ronald L. McKey, MD Stanley W. Pletcher, MD Heath L. Lemley, MD David Brown, MD
192024-008	Andrew Crichton, MD (2003) Ophthalmology Clinic Rockyview Hospital 7007 14 th Street SW Calgary, Alberta T2V 1P9 Canada	None
192024-009	Guy D'Mellow, MD (2991) 135 Wickham Terrace Brisbane, Queensland 4000 Australia	None
192024-009	Harvey DuBiner, MD (2450) Clayton Eye Center 1000 Corporate Center Drive Suite 100 Morrow, GA 30260 USA	Charles W. Fico, MD
192024-008	Denise Dudley, MD (2951) Grendahl Eye Associates 3500 La Touche Street, Suite 240 Anchorage, AK 99508 USA	Marvin Grendahl, MD Robin Grendahl, MD
192024-009	Efraim Duzman, MD (0169) 4605 Barranca Way, Suite 100 Irvine, CA 92604 USA	Eran Duzman, MD
192024-008	Richard Evans, MD (2975) 9150 Huebner Road, Suite 280 San Antonio, TX 78240 USA	Raymond H. Hernandez, III MD

Study Numbers	Principal Investigator Name (Number) and Address	Sub-Investigator(s)
192024-009	Robert Foerster, MD (0207) Colorado Eye Associates 2920 North Cascade Colorado Springs, CO 80907 USA	D.B. Thatcher, MD J. Gregory Baron, MD Michael C. Pharris, OD
192024-009	Jonathan Frantz, MD (2954) 12731 New Brittany Boulevard Fort Myers, FL 33907 USA	None
192024-009	Walter Fried, MD (2860) 3477 Grand Avenue Gurnee, IL 60031 USA	Michael Savitt, MD
192024-009	David Gieser, MD (2958) Wheaton Eye Clinic 2015 North Main Street Wheaton, IL 60187 USA	Jeffrey R. Haag, MD Walter E Hagens, MD Michael Kipp, MD
192024-009	Ivan Goldberg, MD (2005) 187 Macquarie Street, 4 th Floor Sydney, New South Wales 2000 Australia	Stuart Graham, MD
192024-008	Stephen Greenberg, MD (2964) 233 Union Avenue Holbrook, NY 11741 USA	Geoffrey Weismann, MD Michael J. Weiner, MD
192024-008	Ronald Gross, MD (1642) Alkek Eye Center 6565 Fannin #1401 Houston, TX 77030 USA	Silvia Orengo-Nania, MD
192024-008	Neeru Gupta, MD, PhD (2959) St. Michael's Hospital 30 Bond Street Suite 7 – 183, Victoria Wing Toronto, Ontario M5B 1W8 Canada	None
192024-008	Leonard Gurevich, MD (2965) Western New York Eye Care Associates 550 Orchard Park Road, Suite A101 West Seneca, NY 14224 USA	Philip Sarikey, OD Jeffrey J. Calhoun, OD
192024-009	Eve Higginbotham, MD (2869) Department of Ophthalmology Maryland Center for Eye Care 419 West Redwood Street, Suite 420 Baltimore, MD 21201 USA	Ramzi Hemadey, MD Monica Allen, MD

Study Numbers	Principal Investigator Name (Number) and Address	Sub-Investigator(s)
192024-008	Oscar Kasner, MD (1585) Jewish General Hospital Department of Ophthalmology 3755 Côte-Sainte-Catherine Montréal, Quebec H3T 1E2 Canada	None
192024-008	Donald Kellum, MD (2963) Boulder Medical Center 2750 Broadway Boulder, CO 80304 USA	Donald L. McCormack, MD R. William Hilty, MD
192024-008	Melvyn Koby, MD (2966) Doctor's Eye Institute 4004 Dupont Circle Louisville, KY 40207 USA	David W. Karp, MD
192024-008	John Kwedar, MD (2969) Springfield Clinic Eye Institute Saint John's Pavilion 301 North Eighth Street Springfield, IL 62702 USA	Randall Peterson, MD
192024-009	Richard Lewis, MD (0526) 3939 J Street, Suite 102 Sacramento, CA 95819 USA	Monica Robinson, MD
192024-009	Andrew Logan, MD (2992) 94 Dixon Street, 8 th Floor Wellington 6001 New Zealand	None
192024-008	David McGarey, MD (2821) I Care! Eye Care! 710 North Beaver Street Flagstaff, AZ 86001 USA	Tomas Tredici, MD
192024-009	Richard McGovern, MD (2993) Royal Adelaide Hospital North Terrace Adelaide, South Australia 5000 Australia	Anna Galanopoulos Mark Chehade James Walker Richard Fleming Arthur Karagiannis Nandor Jaross Stewart Ross
192024-008	Frederick Mikelberg, MD (0689) I.O.D.E. Glaucoma Centre 2550 Willow Street Vancouver, British Columbia V5Z 3N9 Canada	None
192024-009	Thomas Mundorf, MD (1485) Presbyterian Medical Center 1718 East 4 th Street, Suite 806 Charlotte, NC 28204 USA	None
192024-009	George Nardin, MD (2956) The Windward Eye Clinic 407 Uluniu Street, Suite 214 Kailua, HI 96734 USA	David Randell, MD Peter Roney, MD

Study Numbers	Principal Investigator Name (Number) and Address	Sub-Investigator(s)
192024-008	Robert Noecker, MD (2942) University of Arizona Health Sciences Center 707 North Alvernon, Suite 301 Tucson, AZ 85711 USA	Barton L. Hodes, MD
192024-009	Jonathan Nussdorf, MD (2955) John C. Meyer, MD Jewish Hospital Medical Plaza 100 East Liberty Street Suite 800 and Suite 700 Louisville, KY 40202 USA	John C. Meyer, MD
192024-009	Julian Rait, MD (2666) Royal Victorian Eye & Ear 126 Victoria Parade East Melbourne, Victoria 3002 Australia	Desmond O'Duffy, MD
192024-008	Leon Remis, MD (2896) 1 Widger Road, Suite 108 Marblehead, MA 01945 USA	None
192024-008	Robert Ritch, MD (0226) New York Eye and Ear Infirmary 310 East 14 th Street, Suite 304 New York, NY 10003 USA	Jeffrey M. Liebmann, MD Robert F. Rothman, MD Celso Tello, MD Daniel A. Jewelewicz, MD Raghu Mudumbai, MD
192024-008	Michael Rotberg, MD (2037) Southeast Clinical Research Associates 1600 East Third Street Charlotte, NC 28204 USA	George J. Alter, MD James H. Antoszyk, MD David J. Browning, MD Robert A. Flores, MD Kashkap B. Kansupada, MD Andrew N. Antoszyk, MD John E. Bourgeois, MD Julian C. Culton, MD Scott L. Jaben, MD Timothy J. Saunders, MD Donald H. Stewart, III MD F. Scott Sutherland, MD John E. Weaver, MD John E. Young, MD
192024-008	Howard Schenker, MD (2429) Rochester Ophthalmological Group, P.C. 2100 South Clinton Avenue Rochester, NY 14618 USA	Alan Gruber, MD Paul Hartman, MD Ronald Monacelli, OD
192024-008	Joel Schuman, MD (2110) New England Eye Center 750 Washington Street, Box 450 Boston, MA 02111 USA	None

Study Numbers	Principal Investigator Name (Number) and Address	Sub-Investigator(s)
192024-008	Elizabeth Sharpe, MD (1995) Ophthalmic Research Consortium 1300 Hospital Drive, Suite 370 Mount Pleasant, SC 29464 USA	William C. Stewart, MD David G. O'Day, MD
192024-008	Mark Sherwood, MD (2118) University of Florida College of Medicine Ophthalmology Department Box 10028 1600 SW Archer Road Gainesville, FL 32610 USA	M. Fran Smith, MD J. William Doyle, MD, PhD Michael Morris, MD Guy Angella, MD
192024-009	Robert Shields, MD (1724) 850 East Harvard Avenue, Suite 205 Denver, CO 80210 USA	David S. Pfoff, MD Mark B. Walker, MD
192024-008	Joseph Sokol, MD (2952) OptiCare 87 Grandview Avenue Waterbury, CT 06708 USA	None
192024-008	Alfred Solish, MD (0202) Southern California Glaucoma Consultants 800 Fairmount Avenue, Suite 219 Pasadena, CA 91105 USA	Samuel P. Solish, MD
192024-008	William Stewart, MD (1783) Pharmaceutical Research Corporation 914 Folly Road, Unit C Charleston, SC 29412 USA	Elizabeth Sharpe, MD William Lee, MD
192024-009	Thomas Walters, MD (1634) Keystone Research LTD 1015 W. 34 th Street Austin, TX 78705 USA	Jon Dietlein, MD James Montgomery, MD
192024-008	Julia Whiteside-Michel, MD (2953) Jones Eye Institute/UAMS 4301 West Markham Street, Slot 523 3 rd Floor, Room J306 Little Rock, AR 72205 USA	Gissur Prtursson, MD Richard Harper, MD
192024-009	Jeffrey Whitsett, MD (3185) 1237 Campbell Road Houston, TX 77055 USA	None

Study Numbers	Principal Investigator Name (Number) and Address	Sub-Investigator(s)
192024-009	Jacob Wilensky, MD (0296) University of Illinois at Chicago UIC Eye Center 1855 West Taylor Chicago, IL 60612 USA	Dave Hillman, MD Sriram Sonty, MD Eugene Hiadkey, MD
192024-009	Robert Williams, MD (2710) Taustine Eye Center 1169 Eastern Parkway, #3334 Louisville, KY 40217 USA	Lloyd R. Taustine, MD Brian K. Kritchman, MD
192024-008	Barbara Wirostko, MD (2961) Huntington Medical Group Department of Ophthalmology 180 East Pulaski Road Huntington Station, NY 11746 USA	Richard G. Davis, MD

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Financial Disclosure by Clinical Investigators

Investigator or Subinvestigator Name (Last, First, Middle Initial)	Date	Study Number
Abelson, Mark B., MD	4-19-99	192024-009

Study Phase

- Prestudy
- On-going monitoring (Only to be done for investigators/subinvestigators from whom information has not been previously collected for this study)
- Site close-out
- One year after close-out

Method of Information Collection

- Telephone contact
- Site visit

Question	Response	Comments If yes, describe briefly; If investigator does not provide information, state reason for refusal
1. Have you, your spouse or your dependent children entered into a financial arrangement with Allergan whereby the value of the compensation could be influenced by the outcome of the study?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
2. Have you, your spouse or your dependent children received any significant payments of other sorts (see definitions for clarification, if necessary) totaling more than \$25,000 (US) made on or after February 2, 1999 from Allergan? (Payment of other sorts would include a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, honoraria, etc.)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Through Ophthalmic Research Associates. (Other studies)
3. Do you, your spouse or your dependent children have any proprietary interest in the product being tested?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
4. Do you, your spouse or your dependent children have any equity interest (i.e., Allergan stock) greater than \$50,000 (US)?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

Allergan Representative Obtaining Information:



Version date: March 1999

Office Director's Memorandum for NDA 21-275

NDA # 21-275

March 16, 2001

Name: Lumigan (bimatoprost ophthalmic solution) 0.03%

Sponsor: Allergan Incorporated

Proposed Indication: For the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

Related Drugs: Xalatan (latanoprost ophthalmic solution) NDA 20-597
Rescula (isopropyl unoprostone ophthalmic solution)
NDA 21-214
Travatan (travaprost ophthalmic solution) NDA 21-257

NDA 21-275 is to be approved effective this date. Reports of establishment inspections are not all completed. However, on review, it is my determination that currently-available information from these inspections is compatible with approval of this application; and in accordance with the provisions of FDAMA, Section 119(a)(F), this approval action will not be delayed pending completion of the establishment inspections.

Robert J. DeLap 03/16/01

Robert J. DeLap, M.D., Ph.D.
Director,
Office of Drug Evaluation V

**APPEARS THIS WAY
ON ORIGINAL**

Deputy Division Director's Memorandum for NDA 21-275

NDA #21-275

March 13, 2001

Name: Lumigan (bimatoprost ophthalmic solution)

Sponsor: Allergan Inc.

Proposed Indication(s): Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

Related Drugs: Xalatan (latanoprost ophthalmic solution) NDA 20-597
Rescula (isopropyl unoprostone ophthalmic solution) NDA 21-214
Travatan (travaprost ophthalmic solution) NDA 21-257

Post-marketing Studies:

With the introduction of prostaglandin analogues for ophthalmologic use, adverse events related to pigmented tissues have been described. In an effort to better understand these events and their potential consequences, post-marketing studies have been requested for each New Drug Application that displays these properties.

In Allergan's March 1, 2001, amendment, Allergan committed to conduct a study to evaluate the potential pigmentation in the trabecular meshwork in patients undergoing a trabeculectomy after at least two years of treatment with Travatan and to conduct (or continue current studies) to evaluate the long-term effects of increased pigmentation.

These commitments are consistent with the commitments of the other new drug applications displaying pigmentation properties. Consistent with the approval letters for the other products, the proposed approval letter for this product does not specify these commitments.

Wiley A. Chambers, M.D.
Deputy Division Director

Deputy Division Director's Memorandum for NDA 21-275

NDA #21-275

March 15, 2001

Name: Lumigan (bimatoprost ophthalmic solution)

Sponsor: Allergan Inc.

Proposed Indication(s): Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

Establishment Inspections:

Four facilities are involved in Allergan's NDA 21-275. Two facilities (Allergan Inc., Waco, TX [redacted]) have received Office of Compliance recommendations as acceptable. Two facilities [redacted] are listed as pending in the Establishment Evaluation System.

The inspection of Allergan Pharmaceutical was completed on March 12, 2001, and a FDA Form 483 was issued with inspectional observations. These observations have been reviewed by the Review Division and are not expected to affect the safety or efficacy of the drug product.

The inspection of [redacted] was completed today, March 15, 2001. In a telephone conversation between Marie Fadden (FDA Field Inspection), Shawn Khorshidi (FDA Review Chemist for DAAODP) and Wiley Chambers (Deputy Division Director for DAAODP), Ms Fadden reported that there were no inspectional observations related to bimatoprost or any issues identified that would affect the approvability of the bimatoprost ophthalmic solution.

Recommendation:

It is recommended that NDA 21-275, Lumigan (bimatoprost ophthalmic solution) be approved for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

Wiley A. Chambers, M.D.
Deputy Division Director

MEETING MINUTES

MEETING DATE: March 5, 2001 **TIME:** 3 p.m. **LOCATION:** Teleconference

HFD-550 Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

NDA 21-275

DRUG: Lumigan (bimatoprost ophthalmic solution) 0.03%

Indication: The reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurement over time) to another intraocular pressure lowering medication.

SPONSOR/APPLICANT: Allergan

TYPE of MEETING: Pre-Approval Safety Conference

ODE V OFFICE PARTICIPANTS:

Robert DeLap

REVIEW DIVISION PARTICIPANTS:

Wiley Chambers, William Boyd, Lucious Lim, Michael Puglisi, Jennifer Harris, Joanne Holmes, Raphael Rodriguez

OPDRA PARTICIPANTS:

Julie Beitz, Anne Trontell, Renan Bonnel, Claudia Karwoski, Patrick Guinn

Serious Adverse Events To Be Monitored By OPDRA:

1. Cardiac events
2. Deaths

Additional Comments:

The major safety concerns with this class of drugs are changes in patients' pigmented tissues, which may be permanent. It is unclear at this time what impact these changes may have. Long term follow-up studies, to be performed by the sponsor, have been requested by the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products. The Division does not see a need for either OPDRA or the sponsor to assess whether Lumigan is being prescribed as first line therapy (versus the indicated second-line use). Dr. Chambers believes the potential risks of changes in melanocytes and melanosomes have been sufficiently communicated to practitioners.

MEETING MINUTES – Pre-Approval Safety Conference

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH

EVALUATION OF CLINICAL INVESTIGATOR INSPECTIONS.

DATE: March 1, 2001
NDA 21-275
HFD 550
SPONSOR: Allergan
Product: Lumigan (bimatoprost) 0.03% ophthalmic solution
Chemical
Type: 1
Potential: P
Indications: For the reduction of intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension.
Project
Manager: Michael Puglisi
Medical
Officer: William Boyd

I. Background:

These routine inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which NDA 21-275 approval may be based and to assure that the rights and welfare of the human subjects of those studies were protected. These inspections were conducted in accordance with CP 7348.811, Clinical Investigators, in addition to concentrate in comparing source documents, case report forms (CRFs), and data listings in regard to primary endpoints, adverse drug events reporting and discontinued subjects in these protocols. Sites selected in corroboration between HFD-550 Division medical officer, Dr. Boyd and DSI reviewer, Dr. Jose Carreras.

Name	City	Protocol	CL
David L. Cooke, M.D.	St. Joseph, Michigan	#192024-008-00	NAI
Robert D. Williams, M.D.	Louisville, Kentucky	#192024-009-00	NAI

In addition because this product is a NME a Sponsor/Monitor inspection was conducted using the data from Dr. Richard Lewis of Sacramento, California.

Allergan	Irvine, California	Sponsor/Monitor	NAI*
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Key to Classifications

NAI = No deviation from regulations—

*Based on communication with the District Office Investigator. EIR has not been reviewed.

Site #1
David L. Cooke, M.D.

This investigator enrolled forty subjects. The field investigator examined all records in depth. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appear acceptable.

Site #2
Robert D. Williams, M.D.

This investigator enrolled fifty subjects. The field investigator examined twelve records in depth. Data audit did not reveal any significant discrepancies and/or deficiencies in the conduct of the study. The data collected from this site appear acceptable.

Site #3
The District Office Investigator found no objectionable conditions. The EIR has not been reviewed.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS:

No objectionable conditions were found in the above sites, which would preclude the use of the data submitted in support of pending NDA.

Jose A. Carreras, M.D.

cc:
NDA 21-275
Division File
HFD-47/Currier

**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research**

DATE OF REVIEW: January 24, 2001
NDA# 21-275
NAME OF DRUG: Lumigan (Bimatroprost Ophthalmic Solution) 0.03%
NDA HOLDER: Allergan

To: Karen Midthun, MD
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

Michael Pughsi
Project Manager
HFD-550

I. Final Review

This consult was written for a final review of the proposed proprietary name, Lumigan, regarding potential name confusion with existing proprietary/generic drug names. We originally reviewed the proprietary name, Lumigan, on January 13, 2000 and found it acceptable (consult # 99-091). In addition, the package insert, the bottle label, and the carton labeling were reviewed for possible interventions in minimizing medication errors.

The OPDRA expert panel reviewed all the FDA approved drug names since October 1999 and identified *Levulan* as a possible sound-alike name. *Levulan Kerastick Topical Solution* contains aminolevulinic acid and it is used in photodynamic treatment for actinic keratoses of the face and scalp. The risk of confusing Lumigan, an ophthalmic agent, and *Levulan*, a topical solution for photodynamic treatment, is minimal. Therefore, OPDRA has no objections to the use of the proposed name, Lumigan.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the carton labeling, the bottle label, and the package insert for Lumigan, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error.

CARTON LABELING and CONTAINER LABEL

1. We recommend revising the format of proprietary and established names as follows:

LUMIGAN
(Bimatoprost Ophthalmic Solution)
0.03 %

2. On the Back Panel, we note that the unit of volume is not included with net contents. Revise to read: "Each mL contains: Active:bimatoprost 0.3 mg..."
3. We note that the 3 mL package size is intended to be a professional sample. We would suggest the following:

"Professional Sample: Not for Resale"

III. RECOMMENDATIONS

- A. OPDRA has no objections to the use of the proprietary name, Lumigan.
- B. OPDRA recommends the above labeling revisions that might lead to safer use of the product.

If you have further questions or need clarifications, please contact Hye-Joo Kim at 301-827-0925.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

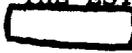
SUBMITTED TO OC 13-OCT-2000 TSOS
SUBMITTED TO DO 13-OCT-2000 GMP EGASM
ASSIGNED INSPECTION '16-OCT-2000 GMP EGASM

Establishment: 

DMF No: AADA:
Responsibilities: FINISHED DOSAGE STERILIZER
Profile: GSP OAI Status: NONE
Estab. Comment: 

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	13-OCT-2000				TSOS
OC RECOMMENDATION	13-OCT-2000			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: 

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment: FOR THIS FACILITY THIS IS THE BULK DRUG SUBSTANCE MANUFACTURING FACILITY. THE CFN # FCCA272 WAS FOUND IN FDA'S DATA BASE, HOWEVER THE ESTABLISHMENT REGISTRATION PROVIDED BY THE NDA APPLICANT IS  (on 02-OCT-2000 by S. TSO (HFD-550) 301-827-2539)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	13-OCT-2000				TSOS
SUBMITTED TO DO	13-OCT-2000	GMP			EGASM
ASSIGNED INSPECTION '16-OCT-2000	GMP				EGASM

APPEARS THIS WAY
ON ORIGINAL