

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: -

21-214

ADMINISTRATIVE DOCUMENTS

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21214/000
Stamp: 15-FEB-2000 Regulatory Due: 15-AUG-2000
Applicant: CIBA VISION
11460 JOHNS CREEK PKY
DULUTH, GA 30097

Priority: 1P
Action Goal:
Brand Name: RESCULA(UNOPROSTONE ISOPROPYL OPHTHALMIC
Established Name:
Generic Name: UNOPROSTONE ISOPROPYL OPHTHALMIC SOLUTIO
Dosage Form: SOL (SOLUTION)
Strength: 0.15%

FDA Contacts: R. RODRIGUEZ (HFD-550) 301-827-2090 , Project Manager
A. FENSELAU (HFD-550) 301-827-2545 , Review Chemist
L. NG (HFD-830) 301-827-2511 , Team Leader

Overall Recommendation:

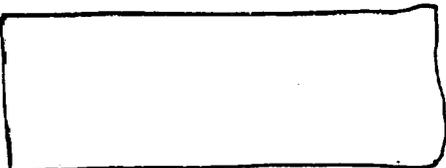
Establishment: 1057836
CIBA VISION OPHTHALMICS
11460 JOHNS CREEK PKY
DULUTH, GA 30097

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-FEB-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment:

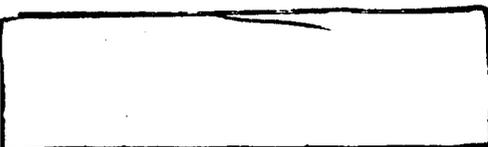


DMF No:
AADA No:

Profile: GSP OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-MAR-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE STERILIZER

Establishment:



DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 14-MAR-2000

Responsibilities: DRUG SUBSTANCE MANUFACTURER

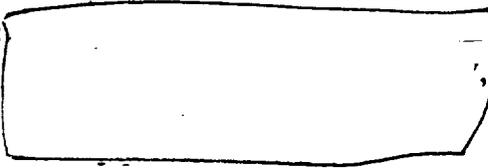
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

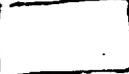
Establishment: 

DMF No: 
AADA No:

Profile: SNI OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-FEB-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE
MANUFACTURER
FINISHED DOSAGE RELEASE
TESTER
FINISHED DOSAGE STABILITY
TESTER

Establishment: 

DMF No: 
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 28-FEB-2000

Responsibilities: DRUG SUBSTANCE
MANUFACTURER
DRUG SUBSTANCE RELEASE
TESTER
DRUG SUBSTANCE STABILITY
TESTER

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21214/000
Stamp: 15-FEB-2000
Regulatory Due: 15-AUG-2000
Applicant: CIBA VISION
11460 JOHNS CREEK PKY
DULUTH, GA 30097
Priority: 1P
Org Code: 550

Action Goal:
District Goal: 16-OCT-2000
Brand Name: RESCULA (UNOPROSTONE ISOPROPYL
OPHTHALMIC
Estab. Name:
Generic Name: UNOPROSTONE ISOPROPYL
OPHTHALMIC SOLUTIO
Dosage Form: (SOLUTION)
Strength: 0.15%

Application Comment: PRIORITY REVIEW HAS BEEN REQUESTED (on 15-FEB-2000 by A. FENSELAU (HFD-550) 301-827-2545)

FDA Contacts: R. RODRIGUEZ (HFD-550) 301-827-2090, Project Manager
A. FENSELAU (HFD-550) 301-827-2545, Review Chemist
L. NG (HFD-830) 301-827-2511, Team Leader

Overall Recommendation:

Establishment: 1057836

CIBA VISION OPHTHALMICS
11460 JOHNS CREEK PKY
DULUTH, GA 30097

*still pending as of 12:30 pm,
7/31/00. CMC*

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: THIS SITE IS THE ALTERNATE SITE FOR DRUG PRODUCT TESTING (RELEASE AND STABILITY TESTING) (on 15-FEB-2000 by A. FENSELAU (HFD-550) 301-827-2545)

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|-------------------|-------------|-----------|------------|--------------------------------|-----------|
| SUBMITTED TO OC | 24-FEB-2000 | | | | FENSELAUA |
| OC RECOMMENDATION | 24-FEB-2000 | | | ACCEPTABLE BASED ON PROFILE | FERGUSONS |

Establishment:



DMF No:

AADA:

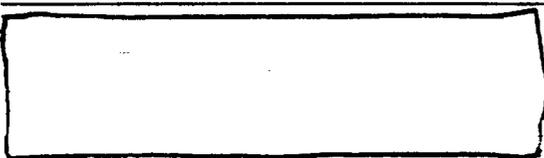
Responsibilities: FINISHED DOSAGE STERILIZER

Profile: GSP OAI Status: NONE

Estab. Comment:

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|-------------------|-------------|-----------|------------|---------------------------------------|------------|
| SUBMITTED TO OC | 24-FEB-2000 | | | | FENSELAUA |
| SUBMITTED TO DO | 29-FEB-2000 | GMP | | | DAMBROGIOJ |
| DC RECOMMENDATION | 01-MAR-2000 | | | ACCEPTABLE BASED ON FILE REVIEW | ADAMSS |
| OC RECOMMENDATION | 02-MAR-2000 | | | ACCEPTABLE DISTRICT RECOMMENDATION | DAMBROGIOJ |

Establishment:



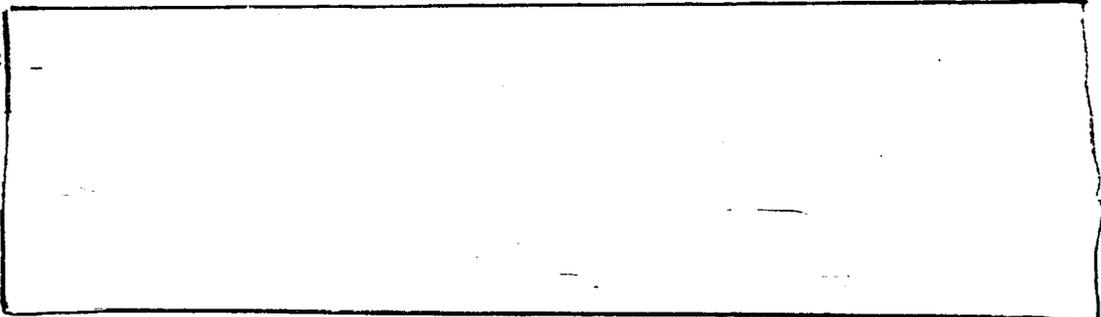
DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment:



| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|----------------------|-------------|-----------|-------------|-------------------|-----------|
| SUBMITTED TO OC | 14-MAR-2000 | | | | FENSELAUA |
| SUBMITTED TO DO | 14-MAR-2000 | GMP | | | EGASM |
| ASSIGNED INSPECTION | 14-MAR-2000 | GMP | | | EGASM |
| INSPECTION SCHEDULED | 29-JUN-2000 | | 07-JUL-2000 | | IRIVERA |
| INSPECTION PERFORMED | 10-JUL-2000 | | 07-JUL-2000 | | EGASM |

Establishment:



DMF No:



AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Profile: SNI OAI Status: NONE

Estab. Comment: THIS WILL BE THE DRUG PRODUCT MANUFACTURER AND PRIMARY (RELEASE AND STABILITY) TESTING SITE (on 15-FEB-2000 by A. FENSELAU (HFD-550) 301-827-2545)

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|-------------------|-------------|-----------|------------|---------------------------------------|-----------|
| SUBMITTED TO OC | 24-FEB-2000 | | | | FENSELAUA |
| SUBMITTED TO DO | 24-FEB-2000 | 10D | | | FERGUSONS |
| DO RECOMMENDATION | 25-FEB-2000 | | | ACCEPTABLE BASED ON FILE REVIEW | ADAMSS |
| OC RECOMMENDATION | 29-FEB-2000 | | | ACCEPTABLE DISTRICT RECOMMENDATION | ADAMSS |

Establishment:



DMF No:

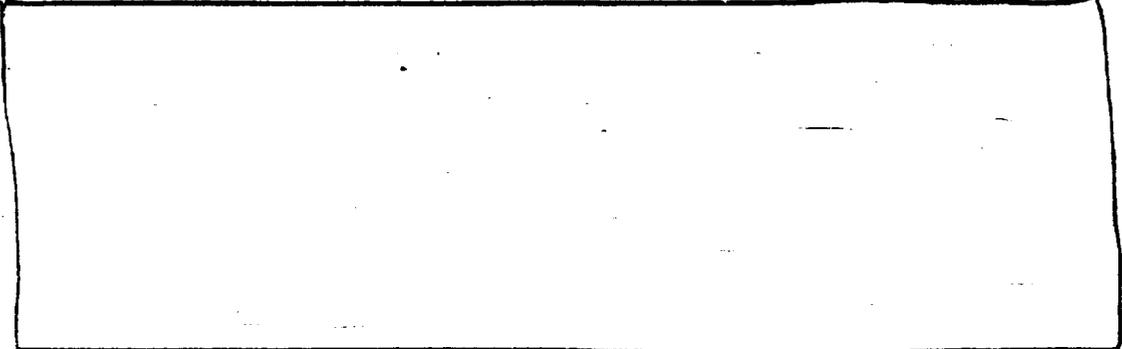


AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Profile: CSN OAI Status: NONE

Estab. Comment:



FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|----------------------|-------------|-----------|-------------|-------------------|------------|
| SUBMITTED TO OC | 25-FEB-2000 | | | | FENSELAUA |
| SUBMITTED TO DO | 28-FEB-2000 | GMP | | | DAMBROGIOJ |
| ASSIGNED INSPECTION | 28-FEB-2000 | GMP | | | ADAMSS |
| INSPECTION SCHEDULED | 29-JUN-2000 | | 13-JUL-2000 | | IRIVERA |
| INSPECTION PERFORMED | 14-JUL-2000 | | 13-JUL-2000 | | EGASM |

APPEARS THIS WAY
ON ORIGINAL

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 | Refer to attached listing of clinical studies and investigators | |
| | covered by this declaration. | |
| | | |

- (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 Timothy Barabe | TITLE Chief Financial Officer |
| FIRM/ORGANIZATION CIBA Vision Corporation | |
| SIGNATURE  | DATE 2/10/2000 |

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

NDA 21-214
Rescula™
(unoprostone isopropyl ophthalmic solution 0.15%)

Attachment to FDA Form 3454

Clinical Investigators

| Investigator | Study (ies) |
|--|------------------------------|
| Allen, Robert, M.D. | C98-UIOS-004 |
| Altman, Bruce, M.D. | C99-UIOS-014 |
| Anand, Nitin | C98-UIOS-011 |
| Barnebey, Howard, M.D. | C98-UIOS-004 |
| Batterbury, Mark | C97-UIOS-005 |
| Baudouin, Christoph | C97-UIOS-010 |
| Berdy, Gregg J., M.D. | C98-UIOS-004 |
| Bibas, Philippe | C97-UIOS-002 |
| Birch, Michael | C97-UIOS-005 C99-UIOS-009 |
| Blixt-Wojechowski, Anita | C97-UIOS-005 C99-UIOS-009 |
| Brogliatti, Beatrice | C98-UIOS-011 |
| Bucci, Massimo Gilberto | C99-UIOS-009 |
| Cacioppo, Leonard, M.D. | C99-UIOS-015 |
| Calel, Bertil | C97-UIOS-005 |
| Campagna, John R., M.D. | C97-UIOS-003 |
| Cantor, Louis B., M.D. | C98-UIOS-004 C97-UIOS-006 |
| Chitkara, Deepak | C98-UIOS-011 |
| Crandall, Alan S., M.D. | C98-UIOS-004 |
| Craven, E. Randy, M.D. | C99-UIOS-015 |
| Davidson, Robert C., M.D. | C97-UIOS-003 |
| Day, Doug, M.D. | C98-UIOS-004 |
| De Graaf-Kret, Catherine Elisabeth Paulina | C97-UIOS-005 |
| De Groot, Veva | C97-UIOS-005 C99-UIOS-009 |
| Dell, Steven, M.D. | C97-UIOS-003 |
| Diamond, Jeremy | C97-UIOS-005 C99-UIOS-009 |
| Dragt, Henk | C97-UIOS-010 |
| Erb, Carl | C98-UIOS-011 |
| Fechtner, Robert T., M.D. | C98-UIOS-004 |
| Flipse, Jan Peter | C98-UIOS-011 |
| Friedlander, Mitchell, M.D. | C98-UIOS-004 |
| Friström, Björn | C97-UIOS-010 |
| Funk, Jens, PD Dr. med. | C97-UIOS-010 |
| Goethals, Marc | C97-UIOS-005 C99-UIOS-009 |
| Grignolo, Federico | C98-UIOS-011 |
| Gross, Ronald L., M.D. | C98-UIOS-004 |
| Gunawardena, Kulasiri | C98-UIOS-013 |
| Hommer, Anton | C98-UIOS-011 |
| Iwach, Andrew G., M.D. | C98-UIOS-004 |
| Kernt, Karin, Dr. med. | C97-UIOS-010 |
| Kisicki, James C., M.D. | C99-UIOS-018 |
| Kolker, Allan E., M.D. | C98-UIOS-004 |
| Laibovitz Robert A., M.D. | C-06-96-001 |
| Lewis, Richard A., M.D. | C98-UIOS-004 |

NDA 21-214
Rescula™
(unoprostone isopropyl ophthalmic solution 0.15%)

Attachment to FDA Form 3454

Clinical Investigators

| Investigators (continued) | Study (ies) |
|-------------------------------|---|
| Liebmann, Jeffrey M., M.D. | C98-UIOS-004 |
| Lindén, Christina | C97-UIOS-010 |
| Lohmann, Chris | C97-UIOS-005 |
| Mandell, Alan I., M.D. | C98-UIOS-004 |
| Melamed, Shlomo | C97-UIOS-005 C99-UIOS-009 |
| Mermoud, Andre | C97-UIOS-005 |
| Meurs, Peter | C97-UIOS-005 C99-UIOS-009 |
| Mundorf, Thomas, M.D. | C-06-96-001 C98-UIOS-004 C97-UIOS-006 |
| Murphy, Paul, M.D. | C98-UIOS-004 |
| Neumann, Ron | C97-UIOS-005 C99-UIOS-009 |
| Nordmann, Jean-Philippe | C97-UIOS-005 C99-UIOS-009 |
| Ober, Manuel | C98-UIOS-011 |
| Orzalesi, Nicola | C97-UIOS-005 C99-UIOS-009 |
| Otto, Peter | C97-UIOS-005 C99-UIOS-009 |
| Patchett, Richard B., M.D. | C99-UIOS-014 |
| Perez, Jordano | C97-UIOS-005 |
| Pfeiffer, Norbert | C97-UIOS-010 C98-UIOS-011 |
| Renard, Jean-Paul | C97-UIOS-005 C99-UIOS-009 |
| Rosen, Paul | C98-UIOS-011 |
| Rotbert, Michael H., M.D. | C98-UIOS-004 |
| Rouland, Jean-Pr. François | C97-UIOS-005 |
| Sall, Kenneth, M.D. | C98-UIOS-004 |
| Samples, John R., M.D. | C98-UIOS-004 |
| Sanchez, Garcia | C97-UIOS-005 C99-UIOS-009 |
| Schölzel, Sonja | C97-UIOS-005 C99-UIOS-009 |
| Schacknow, Paul N., M.D. | C98-UIOS-004 |
| Schmidl, Bernhard | C98-UIOS-011 |
| Schmidt, Karl-Georg, Dr. med. | C97-UIOS-010 C98-UIOS-011 |
| Serle, Janet B., M.D. | C98-UIOS-004 |
| Shah, Sanjay | C97-UIOS-005 |
| Sharpe, Elizabeth, M.D. | C-06-96-001 C97-UIOS-003 C98-UIOS-004 |

NDA 21-214
Rescula™
(unoprostone isopropyl ophthalmic solution 0.15%)

Attachment to FDA Form 3454

Clinical Investigators

| Investigators (continued) | Study (ies) |
|----------------------------------|---|
| Shulman, David G., M.D. | C97-UIOS-003 |
| Simmons, Steven T., M.D. | C98-UIOS-004 |
| Smettan, Reinhard | C97-UIOS-005 C98-UIOS-011 |
| Spencer, Fiona | C97-UIOS-010 |
| Stewart, William C., M.D. | C-06-96-001 C97-UIOS-003 C98-UIOS-004 C98-UIOS-012 |
| Sunaric, Gordana | C97-UIOS-005 |
| Tjia, Khiun Fi | C97-UIOS-010 |
| Veraart, Henk | C97-UIOS-005 C99-UIOS-009 |
| Verdoorn, Cornelis | C98-UIOS-011 |
| Vila, Fernández | C99-UIOS-009 |
| Walters, Thomas R., M.D. | C98-UIOS-004 |
| Wapner, Frances J., M.D. | C97-UIOS-003 |
| Wax, Martin B., M.D. | C98-UIOS-004 |
| Weiss, Mark J., M.D. | C98-UIOS-004 |
| Whitsett, Jeffrey C., M.D. | C98-UIOS-004 |
| Yablonski, Michael, M.D. | C97-UIOS-007 |
| Zeyen, Thierry | C97-UIOS-010 |

**APPEARS THIS WAY
ON ORIGINAL**

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning [redacted] who participated as a clinical investigator in the submitted study 697-0105-024

Name of clinical investigator

Name of

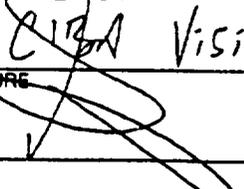
clinical study

is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

| | |
|--|--|
| NAME KEN GREEN | TITLE HEAD, CLINICAL R&D, U.S. |
| FIRM/ORGANIZATION CIQA VISION | |
| SIGNATURE  | DATE FEB. 7, 2000 |

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 4 hours 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:

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

**PATENT INFORMATION
UNDER 21 U.S.C. 355(b)(1)**

U.S. Patent No. **5,001,153** claims a composition including 13,14-dihydro-15-keto-20-ethyl-PGF_{2α} isopropyl ester. The patent claims cover the product, unoprostone isopropyl ophthalmic solution, which is the subject of the New Drug Application filed under 21 U.S.C. §355(b)(1). The date of expiration of the patent is 19 September 2008.

U.S. Patent Nos. **5,151,444**; **5,166,178**; and **5,212,200** claim a composition including a 13,14-dihydro-15-keto-prostaglandin and a method of treating ocular hypertension therewith. The patent claims cover the product, unoprostone isopropyl ophthalmic solution, and the method of using such product, which is the subject of the New Drug Application filed under 21 U.S.C. §355(b)(1). The dates of expiration of the patents are 19 March 2008; 24 November 2009; and 18 May 2010, respectively.

U.S. Patent No. **5,208,256** claims a composition including the combination of 13,14-dihydro-15-keto-loweralkylprostaglandin and a polyoxyethylenesorbitan unsaturated higher aliphatic acid monester and a method of treating ocular hypertension therewith. The patent claims cover the product, unoprostone isopropyl ophthalmic solution, and the method of using such product, which is the subject of the New Drug Application filed under 21 U.S.C. §355(b)(1). The date of expiration of the patent is 21 May 2011.

U.S. Patent No. **5,221,763** claims a composition including 13,14-dihydro-15-keto-PGF. The patent claims cover the product, unoprostone isopropyl ophthalmic solution, which is the subject of the New Drug Application filed under 21 U.S.C. §355(b)(1). The date of expiration of the patent is 22 June 2010.



Authorized Signature for CIBA Vision Corporation
Robert James Gorman, Jr.
Patent Attorney

7 Feb. 2010
Date

d) Did the applicant request exclusivity?

YES /xx/ NO /___/

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

3 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 /xx/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /xx/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 /xx/

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 8. 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 8.

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.

- (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 8:

YES /___/ NO /___/

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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.

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 _____
Title: Medical Officer

June 29, 2000
Date

 / S /

Signature of Division Director _____
Deputy

7/26/00
Date

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 21214 **Trade Name:** RESCULA (UNOPROSTONE ISOPROPYL OPHTHALMIC)

Supplement Number: **Generic Name:** UNOPROSTONE ISOPROPYL OPHTHALMIC SOLUTIO

Supplement Type: **Dosage Form:** SOL

Regulatory Action: AP **Proposed Indication:** Lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

Neonates (0-30 Days) Children (25 Months-12 years)

Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply

Formulation Status

Studies Needed

Study Status _____

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MICHAEL PUGLISI

Signature

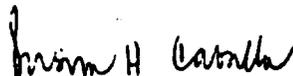
MS/
[Signature]

Date

7/7/2000

DEBARMENT CERTIFICATION STATEMENT

As required under section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, CIBA Vision Corporation - A Novartis Company hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b) of the Act in connection with the New Drug Application for Rescula® unoprostone isopropyl ophthalmic solution, NDA 21-214.

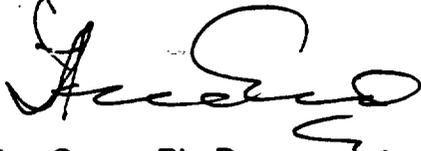

Susan H. Caballa
Vice President, Medical and Regulatory Affairs

2/9/00

Date

GOOD CLINICAL PRACTICE STATEMENT

All clinical studies conducted by or on behalf of CIBA Vision contained in this application were conducted in compliance with Good Clinical practices as per 21 CFR parts 50 and 56 and in the principles of the Declaration of Helsinki.



Ken Green, Ph. D.
Head, Clinical Development

Date 2/9/00

GOOD LABORATORY PRACTICES STATEMENT

As per 21 CFR Part 58 all nonclinical trials were conducted in compliance with Good Laboratory Practices.



Raymond Chau, Ph. D
Director, Global Preclinical Development

Date

2/9/2000

EOP2 MEETING MINUTES

Meeting Date: January 15, 1998

Drug Name: Unoprostone Isopropyl Ophthalmic Solution

Sponsor: Ciba Vision

Type of Meeting: End of Phase 2

Minutes Recorder: Lori Gorski, Project Manager

FDA Attendees:

Michael Weintraub, Wiley Chambers, Andrea Weir, Conrad Chen, Lori M. Gorski, Joanne M. Holmes, M.B.A., Hasmukh Patel, Allan Fenselau, Lillian Patrician, Veneeta Tandon,

CIBA VISION ATTENDEES:

Kim Brazzell, Raymond Chau, Susan Coultas, Marie-Louise Jacques, John Koester, Lawrence D. Mandt, Rick Payor, Kirk Rosemark, Armin Rupp, Ryuji Ueno,

Chemistry/Manufacturing Comments:

FDA Response: *Stability data as presented may not be sufficient to support 12 month shelf life. Particulate matter specifications need to be "less than xx." Analysis of related substances should be refined.*

Question No. 1 (Long Term Toxicology Studies):

CIBA Vision would like to ask the Division whether the long-term toxicology program outlined under Section 1 would fulfil the Division's requirements for the investigation of the long-term preclinical safety for UIOS?

FDA Response: *Acceptable to conduct an additional year long study in both rabbits and monkeys.*

Question No. 2 (Clinical - Pharmacokinetics):

Due to the selection of the 0.15% concentration of UIOS for Phase III clinical trials, CIBA Vision intends to repeat the animal pharmacokinetic study to confirm the previous findings concerning the ocular disposition of the drug. CIBA Vision does not plan to repeat the human pharmacokinetic study that was previously conducted in Japan using 0.12% Rescula. Does the Division concur with this approach?

FDA Response: *Acceptable, assuming full details are provided and the quality of the previous study is acceptable. Encouraged to submit study for review now.*

Question No. 3 (Phase III, Clinical Effectiveness):

Would the Division support CIBA Vision's proposal to define the change of IOP from baseline at 6 months using a mean of four IOP values (morning pre-dose and 2, 8 and 12 hours post-dose) as the primary efficacy end-point for the pivotal studies.

FDA Response: *No. Each time point should be evaluated separately. Minimally these include Baseline, Week 1 or 2, Month 3, Month 6 and Month 12.*

Question No. 4 (Phase III-Clinical Effectiveness):

CIBA Vision plans to use the intent-to-treat sample for the primary analysis and the per-protocol sample for the secondary analysis. Does the Division concur?

FDA Response: *Acceptable.*

Question No. 5 (Statistical Criteria):

Does the Division agree with the proposed primary statistical objective of the Phase III clinical trials as being to determine if UIOS is equivalent to timolol in the US study and to timolol and/or betaxolol in the European study? If so, what would be the regulatory consequences of not demonstrating equivalence to timolol?

FDA Response: *Equivalent to timolol is acceptable [redacted] The potential consequence of not demonstrating equivalence to timolol is the possibility of not demonstrating efficacy.*

Question No. 6 (Phase III, Exclusion Criteria):

CIBA Vision proposes to exclude patients who were previously on a "prostaglandin-like" topical treatment whether currently on the market or undergoing clinical evaluation. Please note that patients previously on UIOS will not be excluded. Does the Division agree with this proposal?

FDA Response: *Acceptable. It is unclear how patients with a history of systemic conditions contraindicated with the use of beta-blockers will be evaluated or if they will be excluded from the labelling of the drug product.*

Question No. 7 (Phase III, Clinical Safety):

It is CIBA Vision's intention to provide endothelial cell count data on 120 patients on test drug (UIOS) after 0, 6, and 12 months exposure. Is it acceptable to the Division that all of the endothelial cell count data will come from the US pivotal study?

FDA Response: *Acceptable.*

Question No. 8 (Phase III, Clinical Safety):

It is CIBA Vision's intention to conduct laboratory assessments for changes in blood chemistry on at least 100 patients on test drug (UIOS) after 0, 6, and 12 months exposure. Is it acceptable to the Division that all of the laboratory assessments will come from the US pivotal study?

FDA Response: *Acceptable.*

Question No. 9 (Clinical Effectiveness):

What clinical criteria/results (e.g., size of clinical program, magnitude of IOP reduction, safety parameters) would be required for a product to be considered for first line therapy in the treatment of chronic open angle glaucoma and ocular hypertension.

FDA Response: *Clinically significant improvement of visual function. Comment: For approval of a first line product with an indication of reducing intraocular pressure, the product should demonstrate IOP reduction levels equivalent or superior to timolol, have an explained mechanism of action and have known explanations and consequences of any ocular findings (for example, iris or lid pigmentation changes).*

Question No. 10 (Phase III, Clinical Safety):

If iris pigmentation effects are not seen in the clinical trials or are seen at similar levels to the timolol or betaxolol control groups or to that indicated by the Japanese post marketing data (less than 1 in 25,000), how will the issue be addressed in the labeling?

FDA Response: *If iris or lid pigmentation, or lash changes are seen at all, labelling would be expected to be the same as the revised labelling expected for latanoprost this year.*

Question No. 11 (General):

CIBA Vision prefers to use the name "Rescula®" as the proprietary name in the US Does the Division have any concerns regarding the use of this name in the US?

FDA Response: *It is currently too early to check for potential name conflicts. There is concern about any references to "rescue" and having two products with the same name that have different formulations, i.e., U.S. and Japanese formulation.*

Lori Gorski

cc:

[Redacted]

DIV FILES

HFD-550/DepDir/Chambers

HFD-550/Clin Rev/Holmes

HFD-550/Pharm/Weir

HFD-550/Chem/Fenselau

HFD-550/CSO/Gorski

HFD-550/PK/Tandon

HFD-550/Stat/Patrician

8/13/83

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 3/2/00

DUE DATE: 4/20/00

OPDRA CONSULT #: 00-0063

TO:

Karen Midthun, M.D.
Director, Division of Anti-Inflammatory Analgesic, and Ophthalmologic Drug Products
HFD-550

THROUGH:

Raphael Rodriguez
Project Manager, DAAODP
HFD-550

PRODUCT NAME:

Rescula
(unoprostone isopropyl
ophthalmic solution) 0.15%

MANUFACTURER: Ciba Vision Corporation

IDA #: 21-214

AFETY EVALUATOR: Peter Tam, RPh.

OPDRARECOMMENDATIONS:

OPDRA has no objections to the use of the proprietary name, Rescula. However, DDMAC has expressed a concern with this name.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

✓ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS

OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/

5/1/2000

Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

5/1/00

Peter Honig, M.D.
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

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

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 4/18/00

NDA#: 21-214

NAME OF DRUG: Rescula
(unoprostone isopropyl ophthalmic solution) 0.15%

NDA HOLDER: Ciba Vision Corporation

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550) on 3/2/00, to review the proposed proprietary drug name, Rescula, in regard to potential name confusion with existing proprietary/generic drug names.

The Labeling and Nomenclature Committee (LNC) has reviewed this proprietary name on 6/7/99, and found the name acceptable.

PRODUCT INFORMATION

Rescula, (unoprostone isopropyl ophthalmic solution), is an intraocular pressure-lowering docosanoid. It is believed to reduce elevated intraocular pressure (IOP), by increasing the outflow of aqueous humor without stimulating prostaglandin receptors or any other known intraocular pressure reducing receptors.

After application to the eye, unoprostone isopropyl is absorbed through the cornea and conjunctival epithelium where it is hydrolyzed by esterases to its biologically active metabolite unoprostone free acid. In humans, the biologically active metabolite unoprostone free acid rapidly enters the systemic circulation, reaching peak plasma concentrations 15 minutes after ocular administration and is subsequently rapidly eliminated. Elimination of unoprostone free acid from human plasma is rapid, with a half-life of 14 minutes. The recommended dosage is one drop in the affected eye (s) twice daily.

Rescula 0.15% will be supplied as 5 mL solution in 7.5 mL polypropylene bottles with a polypropylene dropper tip and a tamper-evident polypropylene overcap.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference-texts^{1,2,3} as well as several FDA databases⁴ for existing drug names which sound alike or look alike to Rescula to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

The panel discussion was conducted on 3/13/00 to gather professional opinions on the safety of the proprietary name, Rescula. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. There were concerns with sound-alike similarity to Acular 0.5% and Rezulin with written orders.

DDMAC found that the proposed name, Rescula, objectionable because it sounds like "rescue" and could be considered fanciful.

The following sound-alike/look-alike drug names were discussed.

| Product Name | Dosage form(s), Generic name | Usual Dose | Observation |
|--------------|---|--------------|-------------|
| Rescula | Ophthalmic soln 0.15% monopropionate-acyclovir | One drop bid | |
| Acular | Ophthalmic soln 0.5% ketorolac tromethamine | One drop qid | *SA |
| Rezulin | 200, 300 and 400mg tablets, troglitazone | 400 mg/day | *LA |

*SA = Sound-alike

*LA = Look-alike

¹ MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

² American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

⁴ Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

These studies were conducted by OPDRA and involved 94 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Rescula with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Rescula (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

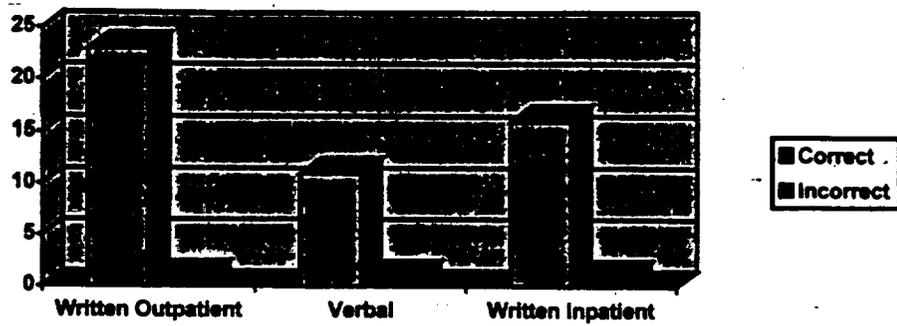
| <u>HANDWRITTEN PRESCRIPTION</u> | <u>VERBAL PRESCRIPTION</u> |
|--|---------------------------------|
| <u>Outpatient RX:</u> Rescula #1 Sig: 1 gtt ou bid | Rescula #1 Sig: 1 gtt ou bid |
| <u>Inpatient RX:</u> Rescula 1 gtt ou bid | |

2. Results:

The results are summarized in Table I.

Table I

| <u>Study</u> | <u># of Participants</u> | <u># of Responses (%)</u> | <u>Correctly Interpreted</u> | <u>Incorrectly Interpreted</u> |
|--------------------|--------------------------|---------------------------|------------------------------|--------------------------------|
| Written Outpatient | 34 | 24 (71%) | 23 | 1 |
| Verbal | 29 | 12 (41%) | 11 | 1 |
| Written Inpatient | 31 | 17 (55%) | 16 | 1 |
| Total | 94 | 53 (56%) | 50 (94%) | 3 (6%) |



Ninety-four percent of the participants responded with the correct name, Rescula. The incorrect written and verbal responses are as follows in Table II.

| | <u>Incorrectly Interpreted</u> |
|--------------------|---|
| Written Outpatient | Ruscula |
| Written Inpatient | Resc |
| Verbal | <u>Phonetic Variable</u> <u>Response</u> |
| | Resculelin |

C. SAFETY EVALUATOR RISK ASSESSMENT

Results of the verbal and written analysis demonstrated 50 participants interpreted the proprietary name, Rescula, correctly. Our studies did not substantiate the concern voiced by the expert panel that Acular and Rezulin might pose potential risks for medication errors due to sound-alike and look-alike similarity. Furthermore, we did not uncover any confusion with overlapping existing approved drug product names.

Rezulin has been recently removed from the market, the potential risk for look-alike confusion between Rescula and Rezulin is no longer exists. However, there is still concern in regard to the potential safety risk between Acular and Rescula due to sound-alike similarity. Rescula and Acular are both ophthalmic solutions and are available in one strength (0.15% vs 0.5%). They can be used in both inpatient and outpatient setting. Rescula has 7 characters length while Acular has 6 and they both share 4 characters "cula". However, Acular is a non-steroid anti-inflammatory agents and is mainly indicated for cataract extraction surgery. The dose schedule for Acular is one drop to affected eye(s) 4 times a day beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the post-operative period. Rescula is, however, indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The recommended dosage for Rescula is one drop to affected eye(s) twice daily.

2. **LABELING, PACKAGING, AND SAFETY RELATED ISSUES:**

We have no comments.

IV. **RECOMMENDATIONS:**

1. OPDRA has no objections to the use of the proprietary name, Rescula.
2. DDMAC found the proposed name, Rescula, objectionable because it sounds like "rescue" and could be considered fanciful.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam at 301-827-3241

/S/ 4/27/00

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/

5/1/2001

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

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: July 7, 2000

NDA 21-214
HFD-550

SPONSOR: Ciba Vision Corporation
Product: Rescula (unoprostone isopropyl ophthalmic solution)
Chemical
Type: 1
Potential: P
Indications: For the reduction of intraocular pressure in patients with chronic open angle
glaucoma or ocular hypertension.

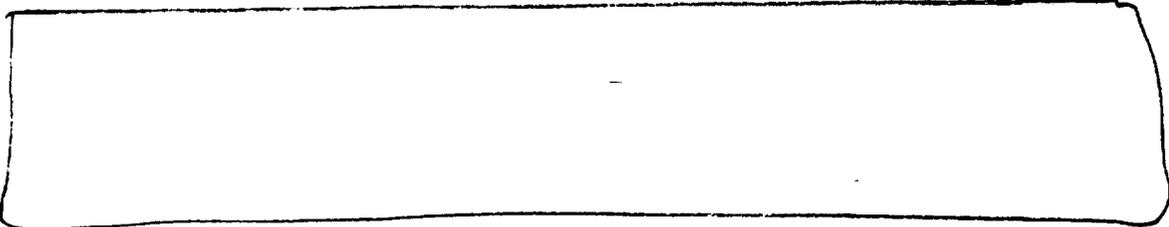
Project Manager: ~~Lori Gorski~~ *Raphel Rodriguez* *WMC 7/27/00*

Medical Officer: ~~Wiley Chambers~~ *William Boyd* *WMC 7/27/00*

I. Background:

These routine inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which NDA 21-214 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. Chambers and DSI reviewer, Dr. Jose Carreras.

| Name | City | Protocol | CL |
|------|------|----------|----|
|------|------|----------|----|



Key to Classifications

NAI = No deviation from regulations

VAI = Minor Deviation(s) from regulations

*Based on communication with the District Office investigators.

Site #1

[REDACTED]

This investigator enrolled forty-two subjects in the study. Thirty -four subjects completed. The field investigator examined 10 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

[REDACTED]

This investigator enrolled 28 subjects in the study. Twenty-three subjects completed. The field investigator examined 10 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

[REDACTED]

"This investigator enrolled 44 subjects. There were only minor deficiencies and no FDA 483 Form was issued".

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS :

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

— Jose A. Carreras, M.D.

cc:
NDA 21-214
Division File
HFD-47/Currier

MEMO OF MEETING

MEETING DATE: July 27, 2000 **TIME:** 11:30am **LOCATION:** Corp. S400

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

NDA 21-214

DRUG: RESCULA (unoprostone isopropyl ophthalmic solution), 0.15%

Proposed Indication: Lowering of 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.

SPONSOR/APPLICANT: Ciba Vision

TYPE of MEETING: Pre-Approval Safety Conference

PARTICIPANTS:

HFD-550: W.Chambers, J.Harris, L.Lim, L.Vaccari, L.Gorski, M.Puglisi, R.Rodriguez,
V.Tandon, A.Fenselau

HFD-430: J.Beitz, A.Trontell, C.Karwoski, R.Bonnel, P.Guinn

Discussion:

The package insert labeling for this product was discussed.

Serious Adverse Events To Be Monitored By OPDRA:

No post-marketing surveillance issues were identified at this time.

The meeting was concluded at 12:05 pm. There were no unresolved issues.