

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-214**

**CHEMISTRY REVIEW(S)**

**Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs  
Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 21-214

**REVIEW #** 1

**DATE REVIEWED:** 30-JUN-00

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original pre-submission	21-DEC-99	22-DEC-99	13-JAN-00
Original submission	14-FEB-00	15-FEB-00	17-FEB-00
Amendment	09-MAR-00	10-MAR-00	16-MAR-00
Amendment	23-MAR-00	24-MAR-99	04-APR-00
Amendment	31-MAR-00	04-APR-99	11-APR-00
Amendment	07-APR-00	10-APR-99	13-APR-00
Amendment	10-APR-00	10-APR-00	13-APR-00
Amendment	17-APR-00	18-APR-00	27-APR-00
Amendment	24-MAY-00	31-MAY-00	08-JUN-00
Amendment	13-JUN-00	14-JUN-00	21-JUN-00
Amendment	13-JUN-00	16-JUN-00	29-JUN-00
Amendment	15-JUN-00	16-JUN-00	29-JUN-00
Amendment	19-JUN-00	20-JUN-00	29-JUN-00
Amendment	21-JUN-00	22-JUN-00	29-JUN-00
Amendment	23-JUN-00	xx-JUN-00	xx-JUN-00
Amendment	27-JUN-00	xx-JUN-00	xx-JUN-00
Amendment	27-JUN-00	xx-JUN-00	xx-JUN-00

**NAME & ADDRESS OF APPLICANT:**

CIBA Vision Corporation  
11460 Johns Creek Parkway  
Duluth, GA 30097-1556

**DRUG PRODUCT NAME**

**Proprietary:** Rescula  
**Established:** Unoprostone isopropyl  
**Code Name/#:** CAS-120373-52-2  
**Chem.Type/Ther.Class:** 1P

**PHARMACOL. CATEGORY:** Lowering of intraocular pressure

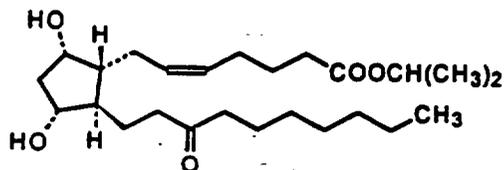
**DOSAGE FORM:** Solution

**STRENGTHS:** 0.15%

**ROUTE OF ADMINISTRATION:** Topical/ocular (1 drop; twice daily)

**DISPENSED:**   X   Rx    OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:**

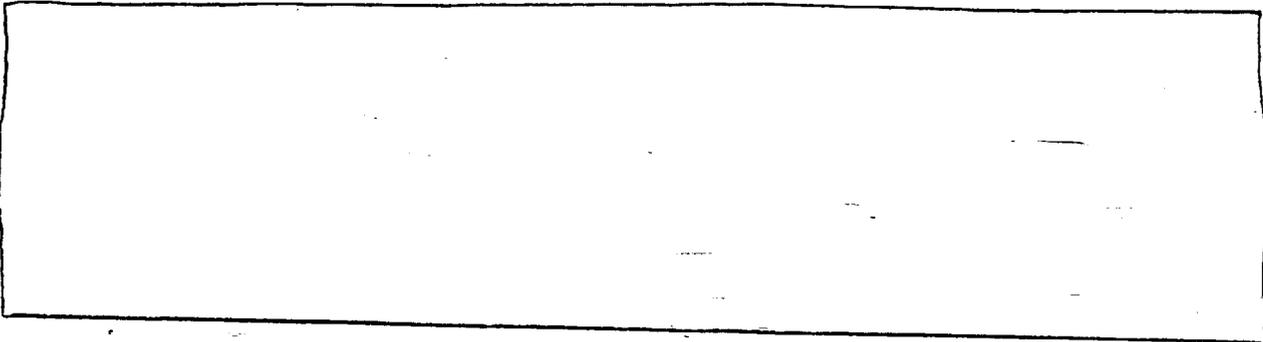


$C_{25}H_{44}O_5$   
M.W.: 424.62

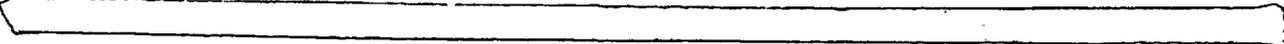
**UNOPROSTONE ISOPROPYL**

Isopropyl (+)-(-)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoate

**SUPPORTING DOCUMENTS:**



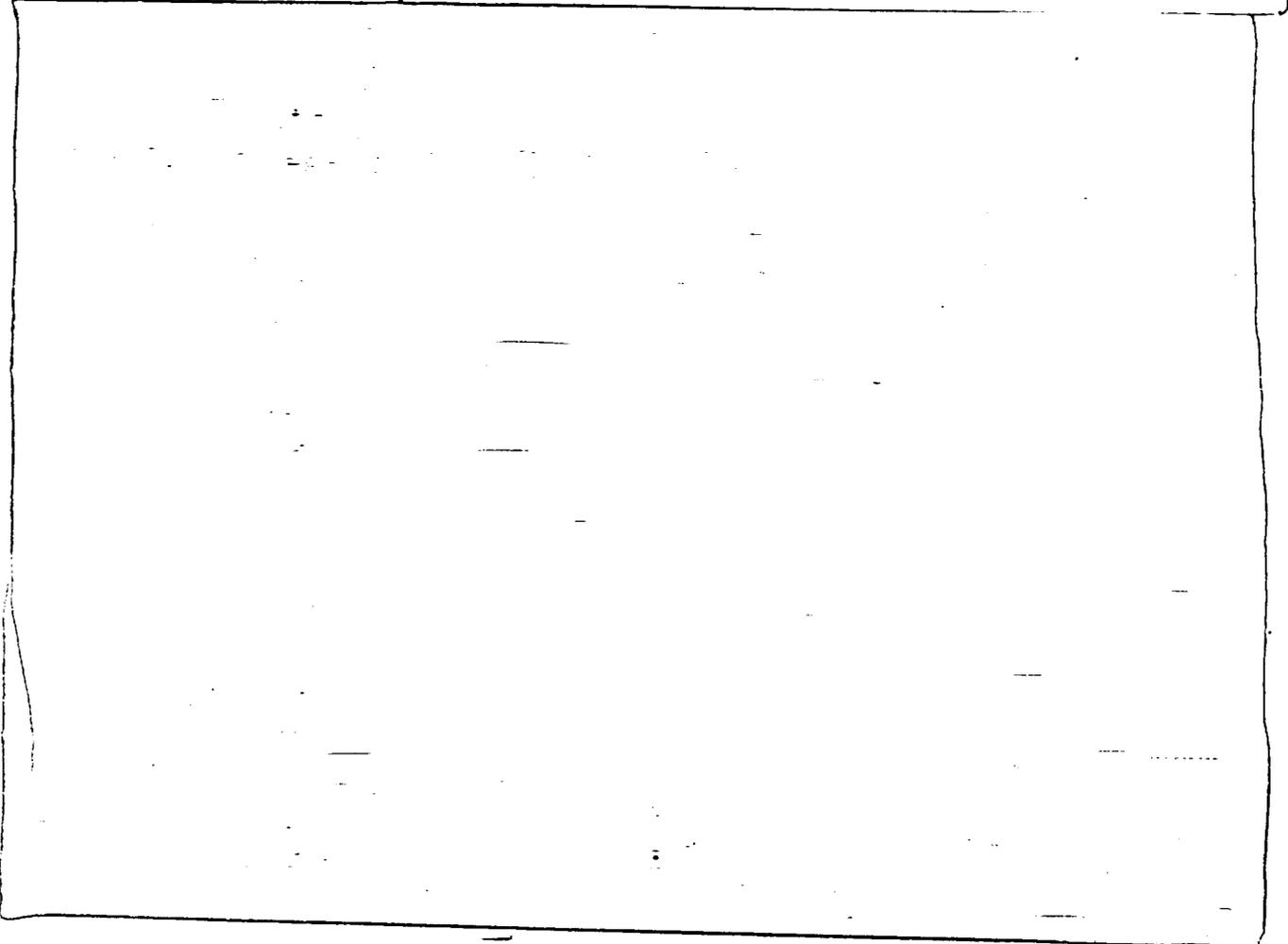
**RELATED DOCUMENTS:**



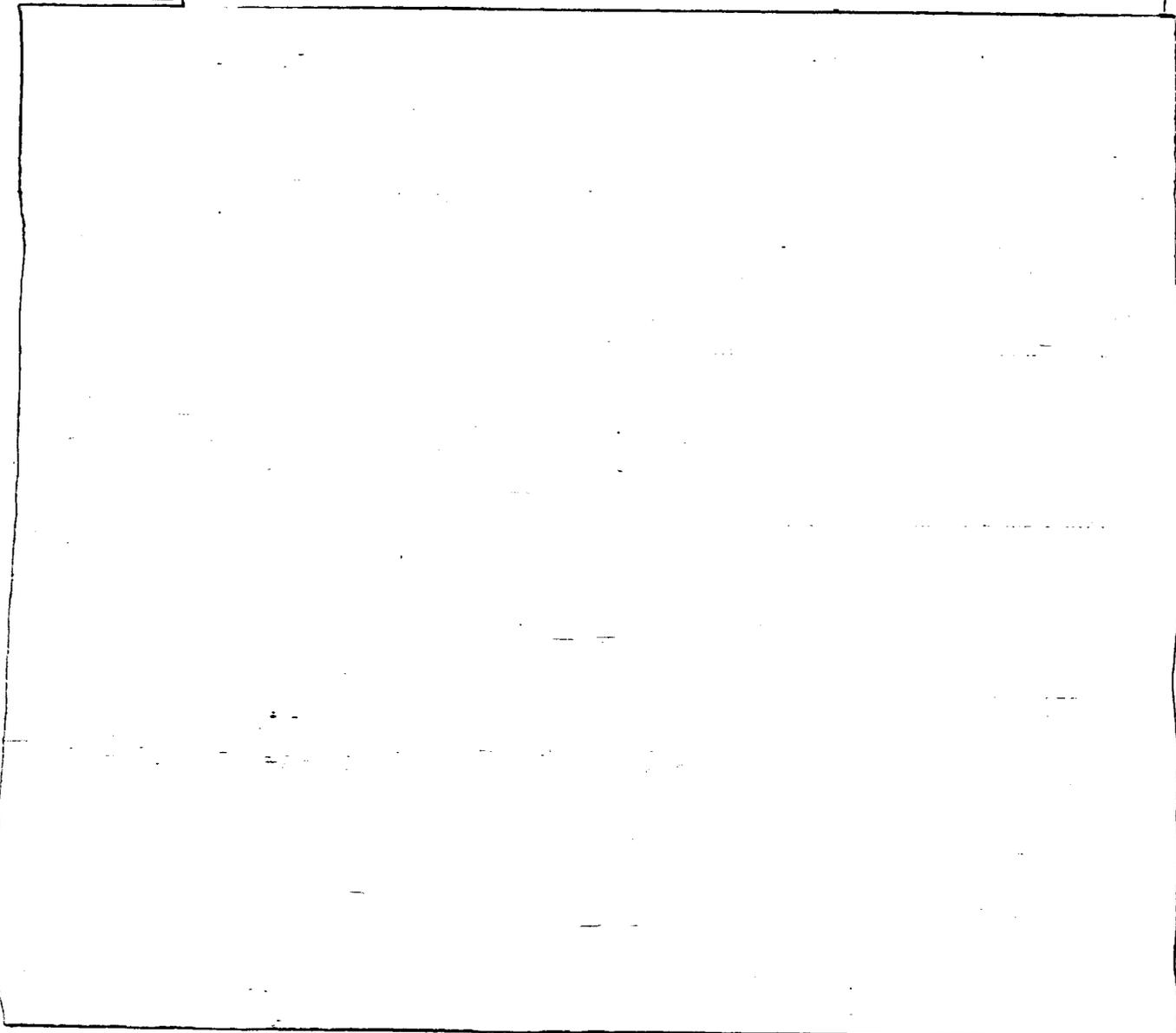
**CONSULT REVIEWS:**

Review of Tradenames (CDER Labeling and Nomenclature Committee, Consult # 00-0063)  
Sterility Assurance Report (N. Sweeney, HFD-160)

**REMARKS: Drug Substance:**



Drug Product:



**CONCLUSIONS & RECOMMENDATIONS:** Based on a review of chemistry, manufacturing and control issues that pertain to the drug substance unoprostone isopropyl and its drug product unoprostone isopropyl ophthalmic solution 0.15% (Rescula®), the application can be approved. Outstanding issues that are needed to complete the review process include: receipt of official copies of three amendments (noted as xx-JUN-00 on first page), submission of the [redacted] and the details of its validation (for use as a regulatory method for the UI drug substance), a satisfactory review of the microbiology issues, and satisfactory cGMP inspections of the Japanese sites.

cc:

- Orig. NDA 21-214
- HFD-550/Division File
- HFD-550/CSO/R.Rodriguez
- HFD-550/Chem/ A.Fenselau
- HFD-550/TeamLdr./L.Ng
- HFD-550/Pharm./
- HFD-550/MO/W.Boyd
- HFD-550/Dep.Div.Dir./W.Chambers
- HFD-830/Div.Dir.DNDCIII/C.-w.Chen

*/S/* 6/30/00

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Allan Fenselau, Review Chemist, HFD-550

*/S/* 6/30/00

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Linda Ng, Chemistry Team Leader, HFD-550

[redacted]

**Division of Anti-inflammatory, Analgesic and Ophthalmic Drugs  
Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 21-214

**REVIEW #** 2

**DATE REVIEWED:** 27-JUL-00

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original submission	14-FEB-00	15-FEB-00	17-FEB-00
Amendment	23-JUN-00	28-JUL-00	xx-JUL-00
Amendment	27-JUN-00	29-JUN-00	06-JUL-00
Amendment	27-JUN-00	29-JUN-00	06-JUL-00
Amendment	24-JUL-00	xx-JUL-00	xx-JUL-00
Amendment	26-JUL-00	xx-JUL-00	xx-JUL-00

**NAME & ADDRESS OF APPLICANT:**

CIBA Vision Corporation  
11460 Johns Creek Parkway  
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**DRUG PRODUCT NAME**

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Established: Unoprostone isopropyl  
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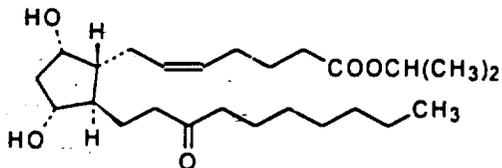
**DOSAGE FORM:** Solution

**STRENGTHS:** 0.15%

**ROUTE OF ADMINISTRATION:** Topical/ocular (1 drop; twice daily)

**DISPENSED:**  Rx  OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:**



$C_{25}H_{44}O_5$   
M.W.: 424.62

**UNOPROSTONE ISOPROPYL**

Isopropyl (+)-(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoate

**REMARKS:** Four issues remained unresolved following the first review of this submission: 1) receipt of official copies of three outstanding amendments, 2) submission by the applicant of the [redacted] (for use as a regulatory method for the unoprostone isopropyl [UI] drug substance), 3) a satisfactory review of the microbiology issues, and 4) satisfactory cGMP inspections [redacted]. Official copies of three amendments have been received (see above listings). [redacted] (for use as a regulatory method for the UI drug substance) will be submitted by 31-OCT-00 to comply with a Phase IV commitment (amendment date 26-JUL-00). The microbiology review signed on 07-JUL-00 recommended approval of the microbiology issues on sterility assurance. Inspections at the two [redacted] sites resulted in the issuance of a Form 483 at each site. The three cGMP deficiencies noted at the [redacted] site involved the lack of a written procedure covering the limit of lots to be included in a campaign and the degree of cleaning between campaign lots, an unprotected light in an area where product

can be exposed, and unlabeled glass vessels in the [redacted] Corrections made during the [redacted] inspection included 1) assurance that an SOP describing campaign production and operating conditions would be created, 2) installation of a sealed light fixture, and 3) assurance that the presence of the unlabeled materials was an isolated instance and remedial training has been given to technical staff to make them better aware of the existing relevant SOP [redacted]

[redacted] Because these deficiencies suggested a lax attitude toward compliance with cGMP (especially with regard to Item 5), additional information was requested by the chemistry reviewer from the applicant in order to verify that the deficiencies identified with Item 5 reflect an isolated incident with no generality to the manufacture [redacted] (for the applicant's responses see the amendments dated 24-JUL-00 and 26-JUL-00). The facility cleaning SOPs [redacted] fail to specify a time limit for completion of facility cleaning after its use, but otherwise are adequate. [redacted]

[redacted] The contractor does not keep a logbook on production room use, but the equipment logbook confirms the use of fully dedicated equipment. The acceptance test results [redacted] were essentially the same for lots produced during the period from 1998 to the present. Release test results for [redacted] which [redacted] displayed no anomalies during the same time period. These findings have been confirmed by the field investigator (who was contacted on 25-JUL-00).

**CONCLUSIONS & RECOMMENDATIONS:** Based on a review of chemistry, manufacturing and control issues that pertain to the drug substance unoprostone isopropyl and its drug product unoprostone isopropyl ophthalmic solution 0.15% (Rescula®), the application can be approved. The issues that were outstanding after Review #1 have been satisfactorily addressed: 1) official copies of three amendments have been received, 2) [redacted]

[redacted] will be submitted in compliance with a Phase IV commitment, 3) the review of the microbiology issues has been forwarded with a recommendation for approval, and 4) cGMP inspections of the [redacted] sites have been performed resulting in the issuance of a Form 483 at each site which identified deficiencies that have been corrected or are correctable. Final approval of this application requires the recommendation from the Office of Compliance on the cGMP issues.

cc:  
Orig. NDA 21-214  
HFD-550/Division File  
HFD-550/CSO/R.Rodriguez  
HFD-550/Chem/ A.Fenselau  
HFD-550/TeamLdr./L.Ng  
HFD-550/Pharm./S.Wilson  
HFD-550/MO/W.Boyd  
HFD-550/Dep.Div.Dir./W.Chambers  
HFD-830/Div.Dir.DNDCIII/C -w.Chen  
[redacted]

*/S/* *7/27/00*  
Allan Fenselau, Review Chemist, HFD-550

*/S/* *7/27/00*  
Linda Ng, Chemistry Team Leader, HFD-550

Concur.  
cGMP issues have been resolved.  
*/S/* *7/27/00*