CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-737

CHEMISTRY REVIEW(S)

NDA 21-737

Retisert

Fluocinolone Acetonate Intravitreal Implant

0.59 mg

Bausch & Lomb, Inc.

Su C. Tso, Ph. D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

HFD-550

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Chemistry Review Data Sheet

1. NDA 21-737

2. REVIEW #: 2

3. REVIEW DATE: April 6, 2005

4. REVIEWER Su C. Tso, Ph.D.:

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-NDA meeting	5/10/04
NDA review #1	3/7/05

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Micro review	3/18/08
EES	4/8/05

7. NAME & ADDRESS OF APPLICANT:

Name: Bausch & Lomb

Address: 8500 Hidden River Parkway, Tampa, FL 33637

Representative: Julie Townsend, MPH

Telephone: 813-866-2299

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Retisert
b) Non-Proprietary Name (USAN): Fluocinolone Acetonide
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Orphon Drug designation

Pursuant to 21 CFR 314.54 and section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act, and the CMA Pilot 1 Program under PDUFA III, Bauch & Lomb submitted new drug application NDA 21-737.

Pursuant to Section 526 of the Federal food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the designation of fluocinolone acetonide as an orphan drug (application #1328). Fast Track designation was granted by FDA on 4/28/00, and orphan Drug designation was granted on 8/3/00, and CMA Pilot program was granted on 1/26/04.

10. PHARMACOL. CATEGORY: Anti-inflammatory

11. DOSAGE FORM: Intravitreal Implant

12. STRENGTH/POTENCY: 0.59 mg/implant

13. ROUTE OF ADMINISTRATION: Intravitreal implantation

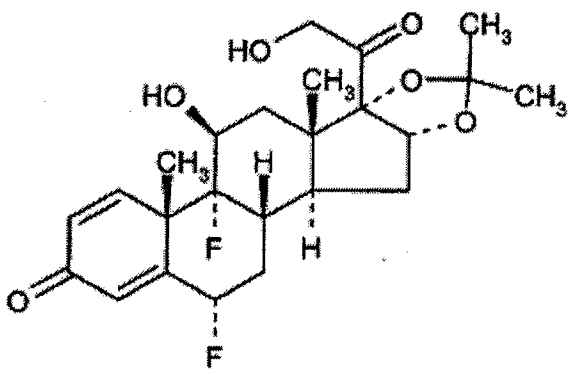
14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

15. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula: $C_{24}H_{30}F_2O_6$ (anhydrous)

Molecular Weight: 452.5

Chirality: See structure above

Relative and Absolute Stereochemistry: See structure above

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS	DATE REVIEW COMPLETED	COMMENTS
	II			3 1	Adequate Adequate	Review # 3 By E. Pappas Review # 4 By Su C. Tso	LOA : 10/20/03
	I			~~2~~	Not reviewed		9/17/04
	IV			1	Adequate	Su Tso Review #1	1/13/05
	III			1	adequate	1/21/05 Su Tso Review # 1	6/1/04

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. Other Documents:

MAF	Holder	Item	Date of LOA
[redacted]	[redacted]	[redacted]	8/28/04
[redacted]	[redacted]	[redacted]	8/28/04

C. IND: #60,000

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Recommended approval	4/6/05	Compliance
Methods Validation	Will not submitted	3/7/05	Su C. Tso
OPDRA	Trade name approved in IND # 60,000	10/5/01	Alina R. Mahmud
DMETs	Trade name Retisert Acceptable	3/30/05	Linda M Wisniewski
EA	Category exemption	11/04	S. Tso
Microbiology	Approval	3/18/05	Vinayak B. Pawar

The Chemistry Review for A/NDA 21-737

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval from a chemistry, manufacturing, and control standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, fluocinolone acetonide (FA), is compendial (USP, Ph.Eur., JP) grade. It has been used in a variety of established, marketed pharmaceutical products in the United States, EU member States, and Japan. Fluocinolone acetonide is a corticosteroid known for its use as an anti-inflammatory agent in the treatment of skin diseases. Corticosteroids have been shown to repress inflammatory symptoms in ocular diseases affecting the posterior segment of the eye, including posterior uveitis.

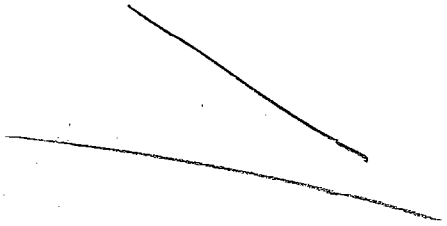
The drug substance is a white or almost white, odorless, crystalline powder. It is insoluble in water but soluble in methanol.

The drug substance will be manufactured by

The drug product is an implant. Each implant contains 0.59 mg fluocinolone acetonide.

The Retisert™ implants are composed of a central core consisting of 0.59 mg of FA : into a tablet. Each FA tablet is encased in a silicone elastomer cup containing a release orifice

between the tablet and the orifice that serves as an additional barrier for drug release from the cup. A suture tab, [redacted] is attached to the silicone cup using silicone adhesive. The suture tab is used to anchor the implant in the eye through a suture hole.



The implants are enclosed in a polycarbonate case placed within a foil pouch which maintains sterility. The implant is further protected from physical impact by a Tyvek pouch. The Tyvek pouch provides a barrier to dirt, dust and particulates while allowing for the user to view the foil pouch labeling. The implants are [redacted] sterilized.

B. Description of How the Drug Product is Intended to be Used

The implants contain 0.59 mg of fluocinolone acetonide and were designed to deliver the drug for up to 1000 days. It is a surgically implanted, polymer-based, sustained-release, intravitreal drug delivery system intended for the treatment of non- infectious posterior uveitis. The product may be approved with an expiration date of 24 months when stored at 15-25 °C.

C. Basis for Approvability or Not-Approval Recommendation

On March 7, 2005, the application was recommended as "approvable" pending for a satisfactory micro review and cGMP inspection at the Waterford, Ireland manufacturing facility.

Since then, microbiologist has recommended approval based on sterility assurance (micro review dated 3/18/05).

cGMP inspection at the Waterford, Ireland facility has been completed. Issues were discussed and resolved by reviewer and investigator. The Office of Compliance recommended approval on 4/6/05.

DDMAC finds the proprietary name Retisert acceptable (Linda M Wisniewski, RN dated 3/30/05).However comments on container labels, carton and package insert labeling of Retisert were provided for possible improvement to minimize potential user error. Refer to review notes.

Therefore, the application is recommended for approval from chemistry, manufacturing, and control standpoint.

III. Administrative

A. Reviewer's Signature

Su C. TSo

B. Endorsement Block

Su C. Tso/Date: 4/6/05
Linda Ng, ChemistryTeamLeader
Raphael Rodriguez, Project Manager

C. CC Block

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On Original

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2 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-_____

NDA 21-737

Retisert

Fluocinolone Acetonide Intravitreal Implant

0.59 mg

Bausch & Lomb, Inc.

Su C. Tso, Ph. D.

Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products

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Chemistry Review Data Sheet

1. NDA 21-737

2. REVIEW #: 1

3. REVIEW DATE: March 3, 2005
Revised on 3/7/05

4. REVIEWER Su C. Tso, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-NDA meeting	5/10/04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	10/7/04
Amendment, BC	1/14/05
Amendment BC	1/31/05
Amendment BC	3/7/05

7. NAME & ADDRESS OF APPLICANT:

Name: Bausch & Lomb

Address: 8500 Hidden River Parkway, Tampa, FL 33637

Representative: Julie Townsend, MPH

Telephone: 813-866-2299

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Retisert
b) Non-Proprietary Name (USAN): Fluocinolone Acetonide
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Orphan Drug designation

Pursuant to 21 CFR 314.54 and section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act, and the CMA Pilot 1 Program under PDUFA III, Bauch & Lomb submitted new drug application NDA 21-737.

Pursuant to Section 526 of the Federal food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the designation of fluocinolone acetonide as an orphan drug (application #1328). Fast Track designation was granted by FDA on 4/28/00, and orphan Drug designation was granted on 8/3/00, and CMA Pilot program was granted on 1/26/04.

10. PHARMACOL. CATEGORY: Anti-inflammatory

11. DOSAGE FORM: Implant

12. STRENGTH/POTENCY: 0.59 mg/implant

13. ROUTE OF ADMINISTRATION: Intravitreal implantation, one implant/eye

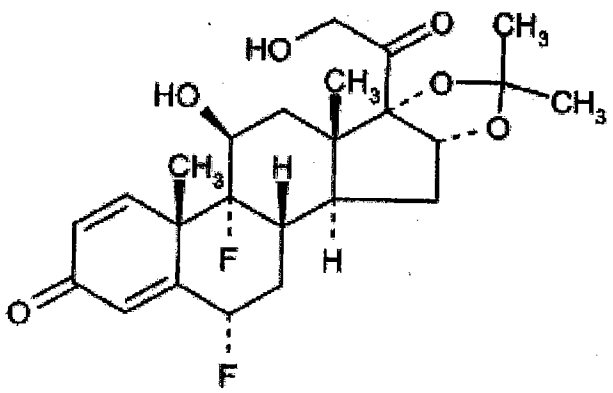
14. Rx/OTC DISPENSED: X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

15. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula: $C_{24}H_{30}F_2O_6$ **(anhydrous)**

Molecular Weight: 452.5

Chirality: See structure above

Relative and Absolute Stereochemistry: See structure above

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS	REVIEW COMPLETED	LOA DATE
	II			3 1	Adequate Adequate	Review # 3 By E. Pappas Review # 4, 1/17/05 By Su C. Tso	10/20/03
	I			2	Not reviewed	none	9/17/04
	IV			1	Adequate	Su Tso Review #2, 2/1/05	1/13/05
	III			1	adequate	Su Tso Review #1, 1/27/05	6/1/04

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7 – Other (explain under "Comments")

B. Other Documents:

MAF	Holder	Item	Date of LOA
[redacted]			8/28/04
[redacted]			8/28/04

C. IND: #60,000

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox	Approval	10/19/04	Conrad Chen
Biopharm	n/a	n/a	n/a
LNC			
Methods Validation	Not submitted	3/3/05	Su Tso
OPDRA	Approved in IND # 60,000 Resubmitted for confirmation	10/5/01	R. Rodriguez on
EA	Category exemption	11/04	S. Tso
Microbiology	Pending		

The Chemistry Review for NDA 21-737

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval from a chemistry, manufacturing, and control standpoint. The final approval is pending from a satisfactory :

1. Microbiology review
2. cGMP inspection of the Waterford, Ireland manufacturing facility

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, fluocinolone acetonide (FA), is compendial (USP, Ph.Eur., JP) grade. It has been used in a variety of established, marketed pharmaceutical products in the United States, EU member States, and Japan. Fluocinolone acetonide is a corticosteroid known for its use as an anti-inflammatory agent in the treatment of skin diseases. Corticosteroids have been shown to repress inflammatory symptoms in ocular diseases affecting the posterior segment of the eye, including posterior uveitis.

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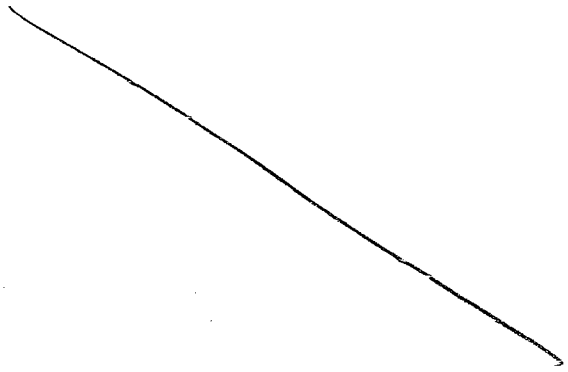

Each implant is individually enclosed in a polycarbonate case placed within a foil pouch which maintains sterility. The implant is further protected from physical impact by a Tyvek pouch. The Tyvek pouch provides a barrier to dirt, dust and particulates while allowing for the user to view the foil pouch labeling. The implants are gamma sterilized.

B. Description of How the Drug Product is Intended to be Used

The implants contain 0.59 mg of fluocinolone acetonide and were designed to deliver the drug for up to 1000 days. It is a surgically implanted, polymer-based, sustained-release, intravitreal drug delivery system intended for the treatment of non-infectious posterior uveitis. The recommended expiration date for the drug product is 24 months when stored at 15-25 $^{\circ}$C.

C. Basis for Approvability or Not-Approval Recommendation

The drug product composes of 0.59 mg fluocinolone acetonate with inactive ingredients being microcrystalline cellulose, magnesium stearate, and polyvinyl acetate. The dosage form is demonstrated to be stable for 24 months under ambient temperature by stability data. Container/closure components were adequately described and qualified. Drug substance and drug product specification were inadequate, and were revised after discussion with the applicant. Analytical control procedures were poorly written, and were modified upon request. Now adequate control procedures are in place at the manufacturing site to ensure quality of the drug substance and the drug product.

The application is recommended for approval from chemistry, manufacturing, and control standpoint pending for a satisfactory microbiology review and a satisfactory inspection of manufacturing facility at Waterford, Ireland.

III. Administrative

A. Reviewer's Signature

Su C. TSo

3/7/05

B. Endorsement Block

Su C. Tso/Date: 3/4/05
Linda Ng, ChemistryTeamLeader/Date
Raphael Rodriguez, ProjectManager/Date

C. CC Block

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X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-_____

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/s/

Su Tso
3/9/05 10:15:36 AM
CHEMIST

Linda Ng
3/9/05 11:20:36 AM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

pplication : NDA 21737/000
Org Code : 550
Priority : 3P

Sponsor: BAUSCH AND LOMB
8500 HIDDEN RIVER PKY
TAMPA, FL 33637

Stamp Date : 08-OCT-2004
PDUFA Date : 08-APR-2005
Action Goal :
District Goal: 07-FEB-2005

Brand Name : RETISERT (FLUOCINOLONE ACETONIDE) 0.59MG
Estab. Name:
Generic Name: FLUOCINOLONE ACETONIDE INTRAVITREAL IMPL
Dosage Form: (CONTROLLED RELEASE TABLET)
Strength : 0.59 MG/IMPLANT

FDA Contacts:			
R. RODRIGUEZ	Project Manager	(HFD-550)	301-827-2090
S. TSO	Review Chemist	(HFD-550)	301-827-2539
L. NG	Team Leader	(HFD-830)	301-827-2511

---

rall Recommendation: ACCEPTABLE on 06-APR-2005by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : 1313525 FEI : 1313525
BAUSCH AND LOMB INC
1400 NORTH GOODMAN ST
ROCHESTER, NY 14609

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STERILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-NOV-04
Decision : ACCEPTABLE
son : BASED ON PROFILE

Establishment : CFN : FEI :
BAUSCH AND LOMB INC
IDA INDUSTRIAL ESTATE, CORK ROAD

WATERFORD, , EI

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : SNI OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-APR-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

Reason : BASED ON PROFILE

Establishment :

[redacted]

DMF No:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-NOV-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment :

[redacted]

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No: AADA:

Responsibilities: [redacted]

Profile : RSP OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-JAN-05

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : [redacted]

DMF No: AADA:

sponsibilities: [redacted]

Profile : CRU OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-NOV-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

rofile : CRU OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-NOV-04

Decision : ACCEPTABLE

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile	: CSN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-NOV-04		
Decision	: ACCEPTABLE		
Reason	: BASED ON PROFILE		