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
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: Orphan Drug designation


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: $\text{C}_{24}\text{H}_{39}\text{F}_{2}\text{O}_{6}$ (anhydrous)
Molecular Weight: 452.5
Chirality: See structure above
Relative and Absolute Stereochemistry: See structure above

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

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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:

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C. IND: #60,000

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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 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 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, Chemistry Team Leader
   Raphael Rodriguez, Project Manager

C. CC Block

Appears This Way
On Original
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

HFD-550
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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
   Pre-NDA meeting
   Document Date
   5/10/04

6. SUBMISSION(S) BEING REVIEWED:

   Submission(s) Reviewed
   Original submission
   Document Date
   Amendment, BC
   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 I 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: $C_{24}H_{30}F_{2}O_{6}$ (anhydrous)
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Chirality: See structure above
Relative and Absolute Stereochemistry: See structure above

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Other codes indicate why the DMF was not reviewed, as follows:
EXECUTIVE SUMMARY SECTION

2 - Type 1 DMF
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6 - DMF not available
7 - Other (explain under "Comments")

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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.

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 Each FA tablet is encased in a silicone elastomer cup containing a release orifice.
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 °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

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

C. CC Block
82 Page(s) Withheld

☐ § 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**

**Application**: NDA 21737/000  
**Sponsor**: BAUSCH AND LOMB  
**Org Code**: 550  
**Priority**: 3P  
**Stamp Date**: 08-OCT-2004  
**Brand Name**: RETISERT (FLUOCINOLONE ACETONIDE) 0.59MG  
**PDUFA Date**: 08-APR-2005  
**Estab. Name**:  
**Action Goal**:  
**District Goal**: 07-FEB-2005  
**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  

----------

**Overall Recommendation**: ACCEPTABLE on 06-APR-2005 by 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**
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

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Milestone Date: 19-JAN-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment :

Responsibilities:

Profile : CRU  OAI Status:  NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-NOV-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment :

Responsibilities:

Profile : CRU  OAI Status:  NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-NOV-04
Decision : ACCEPTABLE
Responsibilities:

Profile: CSN
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-NOV-04
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

OAI Status: NONE