CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201923Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
Cross-Discipline Team Leader Review for NDA 201923 Review #2 - Labeling

Date: September 23, 2014

From: William M. Boyd, M.D.

Subject: Cross-Discipline Team Leader Review #2 - Labeling

NDA #: 201923

Applicant: Alimera Sciences, Inc.

Date of Submission: September 18, 2014

PDUFA Goal Date: September 26, 2014

Type of Application: 505(b)(1)

Name: Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg

Dosage forms / Strength: Intravitreal insert

Indication(s): Treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure

Submitted:
The applicant submitted revised carton and container labeling and a revised package insert on September 18, 2014 (SDN-54). Per the cover letter:

- The carton and lid fonts have been revised so that some letters, particularly the “I” in the established name and the second “I” in the logo, do not have any “thicker” appearing styles.

- The prescribing information was revised per the Agency’s request dated September 5, 2014, to provide baseline best corrected visual acuity (BCVA) in Section 14 Clinical Studies.

Recommendations:

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is recommended for approval for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure with the labeling found in this review (submitted by the applicant on 9/18/14).

William M. Boyd, M.D.
Clinical Team Leader

Reference ID: 3632053

11 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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WILLIAM M BOYD
09/22/2014

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WILEY A CHAMBERS
09/23/2014
1. Introduction

Fluocinolone acetonide, a synthetic glucocorticoid, is an active ingredient currently marketed in topical dermal, otic and ophthalmic products including an ophthalmic product where it is an intravitreal implant. There is no previous marketing experience in the United States with Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg.

Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA). It has been studied in two doses based on the initial release rates of 0.2 or 0.5 μg/day. Based on in vitro and in vivo data, FA is released at gradually decreasing levels over 24 - 36 months depending on the dose. The applicant is seeking approval for the low dose version of Iluvien (0.19 mg) designed to have an initial release rate of 0.25 μg/day. It was anticipated that the lower exposure of FA in the anterior segment would provide a better safety profile while maintaining efficacy.

The current product was developed with a polyvinyl alcohol matrix inside a very tiny tube which can be inserted through a 25 gauge needle attached to a specially designed inserter.

2. Background

Diabetic macular edema (DME), a serious, debilitating disease associated with diabetic retinopathy. Lucentis (ranibizumab injection) is approved for the treatment of DME; the supplemental biologics license application was approved 8/10/2012. Eylea (afiblercept) Injection is also approved for the treatment of DME; the supplemental biologics license application was approved 7/29/2014. Ozurdex (dexamethasone intravitreal implant) was approved for the treatment of DME on 6/28/2014.

For a complete background and discussion regarding regulatory submissions and formal meetings with the applicant, see the Medical Officer’s review, Section 2, finalized 8/22/2014.
On March 26, 2014, the applicant submitted their response to the action taken on October 10, 2013, seeking approval for its 36 month extended daily release formulation of Iluvien. In the March 26, 2014, submission, the applicant responded to FDA’s Complete Response letter and further revised the proposed indication to:

3. CMC
See the CDTL review finalized on 10/17/2013, for summary information on the inserter and polymorph testing.

**DRUG SUBSTANCE:**
From the applicant’s submission dated 6/1/2011:

<table>
<thead>
<tr>
<th>Table 1: Specifications for Fluocinolone Acetonide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
</tr>
<tr>
<td>Physical Appearance</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Identification</td>
</tr>
<tr>
<td>Identification by HPLC</td>
</tr>
<tr>
<td>Specific Rotation</td>
</tr>
<tr>
<td>Loss on Drying</td>
</tr>
<tr>
<td>Assay</td>
</tr>
<tr>
<td>Related Substances</td>
</tr>
</tbody>
</table>
Table 1: Specifications for Fluocinolone Acetonide (Continued)

<table>
<thead>
<tr>
<th>Test</th>
<th>Acceptance Criteria</th>
<th>Analytical Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Unspecified Impurity</td>
<td>Not more than</td>
<td></td>
</tr>
<tr>
<td>Total Impurities</td>
<td>Not more than</td>
<td></td>
</tr>
<tr>
<td>Residual Solvents</td>
<td>Not more than</td>
<td>CTM-200503</td>
</tr>
<tr>
<td>Particle Size(a)</td>
<td>Not less than</td>
<td></td>
</tr>
<tr>
<td>Particle 5(\mu)m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Particle 7(\mu)m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymorphism</td>
<td>Not less than</td>
<td></td>
</tr>
<tr>
<td>Microbial Limits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Aerobic Count</td>
<td>Not more than</td>
<td></td>
</tr>
<tr>
<td>Yeast/Mold Count</td>
<td>Not more than</td>
<td></td>
</tr>
<tr>
<td>Specific Organisms</td>
<td>Absence of S. aureus, E. coli, P. aeruginosa, Salmonella species</td>
<td></td>
</tr>
</tbody>
</table>

DRUG PRODUCT:
From the applicant’s original submission dated 6/30/2010:

Table 1: Composition of Iluvien

<table>
<thead>
<tr>
<th>Amount per Insert</th>
<th>Component</th>
<th>Function</th>
<th>Quality Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.19 mg</td>
<td>Fluocinolone Acetonide</td>
<td>Active Ingredient</td>
<td>USP, Ph. Eur.</td>
</tr>
<tr>
<td></td>
<td>Polyvinyl Alcohol</td>
<td></td>
<td>Manufacturer’s specifications</td>
</tr>
<tr>
<td></td>
<td>Water for Injection</td>
<td></td>
<td>USP</td>
</tr>
<tr>
<td></td>
<td>a Water for Injection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2:

<table>
<thead>
<tr>
<th>Amount per Insert</th>
<th>Component</th>
<th>Function</th>
<th>Quality Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Applicable*</td>
<td>Polymide Tubing</td>
<td></td>
<td>Manufacturer’s specification</td>
</tr>
<tr>
<td></td>
<td>Silicone Adhesive</td>
<td></td>
<td>Manufacturer’s specification</td>
</tr>
</tbody>
</table>
Table 3: Inserter Components

<table>
<thead>
<tr>
<th>Item</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handpiece</td>
<td></td>
</tr>
<tr>
<td>Guideshift</td>
<td></td>
</tr>
<tr>
<td>Needle</td>
<td></td>
</tr>
</tbody>
</table>

From the applicant’s submission dated 6/1/2011:

Table 1: Quality Control Specifications

<table>
<thead>
<tr>
<th>Test</th>
<th>Specification</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>light brown filled tube, no visible deformation</td>
<td>CTM-200341</td>
</tr>
<tr>
<td>Identification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPLC</td>
<td>Retention time of the sample compares to the retention time of the standard within</td>
<td>CTM-200501</td>
</tr>
<tr>
<td>TLC</td>
<td>$R_f$ is the same as Standard</td>
<td>CTM-200507</td>
</tr>
<tr>
<td>Assay – Fluocinolone Acetonide</td>
<td></td>
<td>CTM-200501</td>
</tr>
<tr>
<td>Related Substances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specified Identified and Unidentified Individual Impurity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Release</td>
<td>Not more than (0)(4) μg/day</td>
<td>CTM-200501</td>
</tr>
<tr>
<td>Stability</td>
<td>Not more than (0)(4) μg/day</td>
<td>CTM-200562</td>
</tr>
<tr>
<td>Release</td>
<td>Not more than</td>
<td></td>
</tr>
<tr>
<td>Stability</td>
<td>Not more than</td>
<td></td>
</tr>
<tr>
<td>Unspecified Individual Impurity</td>
<td>Not more than μg/day</td>
<td>CTM-200501</td>
</tr>
<tr>
<td>Release</td>
<td>Not more than</td>
<td></td>
</tr>
<tr>
<td>Stability</td>
<td>Not more than</td>
<td></td>
</tr>
<tr>
<td>Total Impurities</td>
<td>Not more than</td>
<td></td>
</tr>
<tr>
<td>Release Rate</td>
<td>μg/day</td>
<td>CTM-200502</td>
</tr>
</tbody>
</table>
Table 1: Quality Control Specifications (Continued)

<table>
<thead>
<tr>
<th>Test</th>
<th>Specification</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxin</td>
<td></td>
<td>PTS-200566</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MTM-200033</td>
</tr>
<tr>
<td>Sterility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stability – Container Closure Integrity</td>
<td>Conforms</td>
<td>EPS-SOP-SAS-093</td>
</tr>
</tbody>
</table>

From CMC review finalized 9/24/2013:

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg.

The new proposed acceptance criteria of \( (0.0) \mu g/day \) for drug product \textit{in-vitro} release rate was found acceptable by Dr. Tapash Ghosh (ONDQA Biopharmaceutics) in his review.

EES Report

From CMC review finalized 8/6/2014:

Office of Compliance has made an overall recommendation as “Acceptable” for the facilities. Therefore, from the CMC perspective, this NDA is recommended for \textbf{Approval}.
<table>
<thead>
<tr>
<th>Application</th>
<th>NDA 201923/000</th>
<th>Action Goal:</th>
<th>District Goal: 20-JUL-2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stamp Date</td>
<td>06-JUN-2010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulatory</td>
<td>26-SEP-2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Applicant</td>
<td>ALIMERA SCIENCES INC</td>
<td></td>
<td>FLUOCINOLONE ACETONIDE INTRAVITREAL INSERT</td>
</tr>
<tr>
<td>Brand Name</td>
<td></td>
<td>Estab. Name:</td>
<td>ALPHARETTA, GA 30005</td>
</tr>
<tr>
<td>Generic Name</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Priority</td>
<td>3</td>
<td>Product Number:</td>
<td>001; INSERT: FLUOCINOLONE ACETONIDE, 1.0 MG</td>
</tr>
<tr>
<td>Org. Code</td>
<td>500</td>
<td>Dosage Form:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ingredient:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Strengths:</td>
<td></td>
</tr>
</tbody>
</table>

**Application Comment:**
- NEW DRUG APPLICATION-PRIORITY (on 13-JUL-2010 by A. CUFF (HF-01) 3017964061)
- NEW DRUG APPLICATION-PRIORITY (on 13-JUL-2010 by A. CUFF (HF-01) 3017964061)
- NEW DRUG APPLICATION-PRIORITY (on 13-JUL-2010 by A. CUFF (HF-01) 3017964061)
- NEW DRUG APPLICATION-PRIORITY (on 13-JUL-2010 by A. CUFF (HF-01) 3017964061)

**FDA Contacts:**
- Z. LI Facility Reviewer 3017961786
- L. QI Prod Qual Reviewer 3017961436
- S. FONG Micro Reviewer (HFQ-003) 3017961501
- N. BHANDARI Product Quality PM 2404023815
- D. WILLARD Regulatory Project Mgr 3017960003
- L. NG Team Leader (HFQ-320) 3017961426

**Overall Recommendation:**
- ACCEPTABLE on 20-JUL-2014 by T. SHARP 3017965205
- PENDING on 12-MAY-2014 by EES_PROD
- WITHHOLD on 11-OCT-2013 by J. WILLIAMS 3017964196
- PENDING on 21-SEP-2013 by EES_PROD
- PENDING on 08-AUG-2013 by EES_PROD
- PENDING on 15-JUL-2013 by EES_PROD
- PENDING on 23-MAY-2013 by EES_PROD
- PENDING on 22-MAY-2013 by EES_PROD
- ACCEPTABLE on 09-NOV-2011 by EES_PROD
- PENDING on 11-JUL-2011 by EES_PROD
- ACCEPTABLE on 23-JUN-2011 by EES_PROD
- PENDING on 24-MAY-2011 by EES_PROD
- WITHHOLD on 15-DEC-2010 by EES_PROD
**FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT**

**Establishment:**
- CFN: (b)(4)
- FEE: (b)(4)
- AADA:

**DMF No:**

**Responsibilities:**
- FINISHED DOSAGE LABELER
- FINISHED DOSAGE MANUFACTURER
- FINISHED DOSAGE RELEASE TESTER
- FINISHED DOSAGE STABILITY TESTER

**Establishment Comment:**
- (b)(4) (on 11-JUL-2011 by A. CUFFA (HF-01))

**Profile:**
- NOT ELSEWHERE CLASSIFIED

**OAI Status:**
- NONE

<table>
<thead>
<tr>
<th>Milestone Name</th>
<th>Milestone Date</th>
<th>Request Type</th>
<th>Planned Completion</th>
<th>Decision</th>
<th>Creator</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAI Submit To OC</td>
<td>14-JUL-2010</td>
<td></td>
<td></td>
<td></td>
<td>CUFFA</td>
</tr>
<tr>
<td>Request to Extend Re-eval Date To</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extension Request</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SUBMITTED TO OC:**
- 14-JUL-2010
- CUFFA

**SUBMITTED TO DO:**
- 26-JUL-2010
- GMP Inspection
- STOCKMI

**ASSIGNED INSPECTION TO IB:**
- 27-JUL-2010
- Product Specific and GMP Inspection
- CEVERLY

**INSPECTION SCHEDULED:**
- 04-AUG-2010
- 27-AUG-2016

**INSPECTION PERFORMED:**
- (b)(4)
- CEVERLY

**DO RECOMMENDATION:**
- 05-NOV-2010
- WITHHOLD
- CEVERLY

PLEASE SEE EIR FOR DETAILS. EIR + EXHIBITS WAS EMailed TO CDER PAIPROGRAM ON 11/3/10.

CARYN MCNAB, PAI MANAGER

**OC RECOMMENDATION:**
- 15-DEC-2010
- WITHHOLD
- CRUZC

CDER OC CONCOURS WITH DISTRICT WITHHOLD RECOMMENDATION. THE MAIN ISSUES FOR THE WITHHOLD ARE: (1) THE LACK OF COMPLETE MANUFACTURING AND CONTROL INSTRUCTION IN THE MASTER PRODUCTION RECORD (MPR); (2) INCOMPLETE TESTING METHOD VALIDATION/VERIFICATION, AND (3) INADEQUATE (b)(4) AND INADEQUATE (b)(4)

**SUBMITTED TO OC:**
- 24-MAY-2011
- CUFFA

**SUBMITTED TO DO:**
- 24-MAY-2011
- 10-Day Letter
- TOULOUSEM

**DO RECOMMENDATION:**
- 20-JUN-2011
- ACCEPTABLE
- CEVERLY

THE FIRM'S RESPONSE WAS FOUND TO BE ADEQUATE (b)(4) NOW RECOMMENDS APPROVAL.
<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Product Specific and GMP Deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>23-Jun-2011</td>
<td>OC Recommendation</td>
<td>Acceptable</td>
</tr>
<tr>
<td>22-May-2013</td>
<td>Submitted to OC</td>
<td>Prabhakaran</td>
</tr>
<tr>
<td>23-May-2013</td>
<td>Submitted to DO</td>
<td>GMP inspection</td>
</tr>
<tr>
<td></td>
<td>Overdue for GMP inspection</td>
<td>Prabhakaran</td>
</tr>
<tr>
<td></td>
<td>Also, clarification of profile class needed (6) for Intravitreal - is this correct?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inspection performed</td>
<td>Ceverly</td>
</tr>
<tr>
<td>19-Aug-2013</td>
<td>Do Recommendation</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>An inspection performed</td>
<td>Ceverly</td>
</tr>
<tr>
<td></td>
<td>NDA 201-023 (Iluvien)</td>
<td>Inadequate validation and/or transfer for DP release and stability methods, release and stability method (6) No uniformity of dosage units performed, no justification (6) for release testing, change of release rate from finished product (6) For rejection action limits, no procedure to create, change or control the Iluvien insert defect challenge (3) If Iluvien, failure to establish reliability of suppliers (6) of fluocinolone acetonide API, polymer, alcohol and silicon adhesive used in the manufacture of Iluvien, inadequate quality assurance (6) Not all inclusive, please see FDA-483 for complete list of deficiencies (6) Not all inclusive, please see FDA-483 for complete list of deficiencies (6) Recommends Withhold of NDA 201-023 and WIL.</td>
</tr>
<tr>
<td>11-Oct-2013</td>
<td>OC Recommendation</td>
<td>Withhold</td>
</tr>
<tr>
<td>12-May-2014</td>
<td>Submitted to OC</td>
<td>Prabhakaran</td>
</tr>
<tr>
<td>12-May-2014</td>
<td>Submitted to DO</td>
<td>10 Day Letter</td>
</tr>
<tr>
<td></td>
<td>Please update the final inspection result (3) the last inspection was conducted (3)</td>
<td></td>
</tr>
<tr>
<td>12-May-2014</td>
<td>Do Recommendation</td>
<td>Withhold</td>
</tr>
<tr>
<td></td>
<td>Continues to recommend withhold of this application due to product specific deficiencies. The firm's response did not provide any additional information that would change the withhold recommendation made on 8/19/2013 after the product specific PA and GMP performed. (3) CDER concurrence memo supporting the district recommendation was issued on 10/14/2013. An NTL was sent to the firm. (3) See CMS Case (3). The current AC status for profile class NEC applies only to commercial products with the same profile class. NDA 201-023 remains unacceptable due to product specific deficiencies.</td>
<td></td>
</tr>
<tr>
<td>Milestone Name</td>
<td>Milestone Date</td>
<td>Request Type</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>--------------</td>
</tr>
<tr>
<td>SUBMITTED TO OC</td>
<td>14-JUL-2010</td>
<td></td>
</tr>
<tr>
<td>SUBMITTED TO DO</td>
<td>20-JUL-2010</td>
<td>GMP Inspection</td>
</tr>
<tr>
<td>ASSIGNED INSPECTION TO DO</td>
<td>20-JUL-2010</td>
<td>GMP Inspection</td>
</tr>
<tr>
<td>INSPECTION PERFORMED</td>
<td>(0)(4)</td>
<td>(0)(4)</td>
</tr>
</tbody>
</table>

The systems covered during the current inspection include: Quality, Production, Facility & Equipment, Materials Management and Laboratory. Deficiencies observed during the inspection resulted in a 3 item FDA-483 issued. The deficiencies cited included:

Firm's management committed to corrective action, and promised a written response to the FD-483.

Recommendations: Review firm's response, classify VAI and approve all applications.

OC RECOMMENDATION | 15-DEC-2010 | WITHHOLD | CRUZC |

A REQUEST FOR ADDITIONAL INFORMATION WAS SENT TO THE FIRM. THE RESPONSE IS NEEDED TO EVALUATE SITE ADEQUACY TO MANUFACTURE THE PRODUCT.

SUBMITTED TO OC | 24-MAY-2011 | CUFFA |

OC RECOMMENDATION | 24-MAY-2011 | ACCEPTABLE | TOULOUSEM |

SUBMITTED TO OC | 22-MAY-2013 | BHANDARIN |
## FDA CDER EES

**ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT**

### OC RECOMMENDATION
- **Date:** 20-MAY-2013
- **Status:** ACCEPTABLE
- **Signer:** PRABHAKARAN

### SUBMITTED TO DO
- **Date:** 21-SEP-2013
- **Action:** GMP Inspection
- **Note:** RESUBMITTING EER SINCE RE-EVAL IS 9/23. PDUFA IS 10/17/13.
- **Signer:** WILLIAM JU

### ASSIGNED INSPECTION TO ID
- **Date:** 24-SEP-2013
- **Action:** GMP Inspection
- **Signer:** ROSE

### ID RECOMMENDATION
- **Date:** 01-OCT-2013
- **Status:** ACCEPTABLE
- **Comment:** BASED ON FILE REVIEW, [ ] WAS COVERED ON MOST RECENT INSPECTION
- **Signer:** PHILIPYE

### OC RECOMMENDATION
- **Date:** 01-OCT-2013
- **Status:** ACCEPTABLE
- **Signer:** WITTORFR

### SUBMITTED TO OC
- **Date:** 12-MAY-2014
- **Signer:** BHANDARIN

### OC RECOMMENDATION
- **Date:** 12-MAY-2014
- **Status:** ACCEPTABLE
- **Signer:** RHX

---

**Establishment:**
- **CFN:** [ ] (4)
- **FBI:** [ ] (4)
- **Other:** [ ] (4)

**DMF No.:** AADA:

**Responsibilities:**
- **DRUG SUBSTANCE:** [ ] (4)
- **DRUG SUBSTANCE OTHER TESTER**

**Establishment Comment:**
- **Profile:** [ ] (4)
- **OAI Status:** NONE

**Milestone Name** | **Milestone Date** | **Request Type** | **Planned Completion** | **Decision** | **Creator**
---|---|---|---|---|---
OAI Submit To OC | 15-JUL-2013 |  |  |  | BHANDARIN
OC RECOMMENDATION | 16-JUL-2013 |  |  | ACCEPTABLE | SHARPT
SUBMITTED TO OC | 12-MAY-2014 |  |  |  | BHANDARIN
OC RECOMMENDATION | 12-MAY-2014 |  |  | ACCEPTABLE | RHX
OC RECOMMENDATION | 28-JUL-2014 |  |  | ACCEPTABLE | SHARPT

**Reference ID:** 3630039
CDTL Review
William M. Boyd, M.D.
NDA 201923
Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg

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**FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT**

**Establishment:**
- **CFN:**
- **FB:**

**DMF No:**
- **AADA:**

**Responsibilities:**
- **DRUG SUBSTANCE OTHER TESTER:**

**Establishment Comment:**
- (0) (4) ANALYSIS OF DRUG SUBSTANCE on 09-MAY-2014 by N. BHANDARI (9) 2404023815

**Profile:**
- CONTROL TESTING LABORATORY
- **OAI Status:**
- **NONE**

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**Milestone Name** | **Milestone Date** | **Request Type** | **Planned Completion** | **Decision** | **Creator**
--- | --- | --- | --- | --- | ---
OAI Submit To OIC | 11-JUL-2011 | 11-JUL-2011 | GMP Inspection | | CUFFA

**SUBMITTED TO DO:**
- 12-JUL-2011
- UNTITLED LETTER ISSUED AFTER (0) (4) INSPECTION

**ASSIGNED INSPECTION TO BI:**
- 24-JUL-2011
- GMP Inspection

**INSPECTION PERFORMED**
- (0) (4)

**INSPECTION SCHEDULED**
- 04-NOV-2011
- (0) (4)

**DO RECOMMENDATION**
- 09-NOV-2011
- ACCEPTABLE

**OC RECOMMENDATION**
- 09-NOV-2011
- ACCEPTABLE

**SUBMITTED TO OC:**
- 22-MAY-2013

**OC RECOMMENDATION**
- 23-MAY-2013
- ACCEPTABLE

**OTHER TESTER (AS INDICATED IN FORM 356h) = (0) (4) ANALYSIS OF THE DRUG SUBSTANCE**

**SUBMITTED TO OC:**
- 12-MAY-2014

**OC RECOMMENDATION**
- 12-MAY-2014
- ACCEPTABLE

Reference ID: 3630039
4. Nonclinical Pharmacology/Toxicology

The original Pharmacology Toxicology Review finalized 11/17/10 recommended approval of the application.

5. Clinical Pharmacology/Biopharmaceutics

From the ONDQA (Biopharmaceutics) Review finalized 9/23/13:
During the early stages of development, pSivida set a release rate specification of \( (\text{mg/day}) \). This was the release rate specification for all the lots used in nonclinical and clinical studies. On 22 December 2010, the Agency issued a Complete Response Letter and noted that the current specification of \( (\text{mg/day}) \) was not acceptable.

The applicant proposed in this March 27, 2013, resubmission that the new proposed specification for release rate be \( (\text{mg/day}) \). The drug product in-vitro release specification is listed in the drug product specification and will be routinely tested for stability. This specification is acceptable for stability and the applicant’s request \( (\text{mg/day}) \) is acceptable by the Agency.

<table>
<thead>
<tr>
<th>Test</th>
<th>Acceptance Criteria</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release Rate</td>
<td>( (\text{mg/day}) )</td>
<td>CTM-200502</td>
</tr>
</tbody>
</table>

Overall, the resubmission of the proposed Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is acceptable from the biopharmaceutics point of view.

### 6. Sterility Assurance

Per the original Product Quality Microbiology review completed on 12/8/10:

The application is recommended for approval from a microbiology quality standpoint. There are no outstanding product quality deficiencies.

### 7. Clinical/Statistical - Efficacy

In March 2014, the applicant proposed the following revised indication:

The likely rise in intraocular pressure represents a separate safety risk. To the extent that it can be predicted, it is best predicted by prior use of corticosteroids. Work by Mansour Armaly, MD and others...
approximately 50 years ago demonstrated genetic factors were associated with predicting IOP elevations following corticosteroid use. Prior corticosteroid use is usually considered the best predictor of future elevated IOP following corticosteroid use.

The Agency therefore recommended that the applicant’s proposed indication be modified to the following:

ILUVIEN contains a corticosteroid and is indicated for the treatment of diabetic macular edema in patients that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

The revised indication will allow clinicians to assess the response of a previously administered corticosteroid.

The complete response also addressed the Agency observation that 11/58 or approximately 19% of the observer questionnaires in an observation study noted that there were observed difficulties with study drug administration. The applicant responded that they had received marketing authorization for Iluvien in several countries in Europe in 2012 and the product was launched in the United Kingdom and Germany in the spring of 2013. As part of the product launch, hands-on training was provided to the physicians along with a training kit which included an applicator (without an implant) with a 25-gauge needle, an illustrated Administration Guide, an animated Administration DVD and a Practice Eye.

For the period ending January 31, 2014, at least units of Iluvien were used that contained the European Union instructions. Of the units of Iluvien administered with the new instructions, 9 technical complaints were received for a technical complaint rate of 3.3%. This is a notable improvement over the technical complaint rate of 19% for issues observed with administration in the physician utilization study provided in the information to the FDA.

For the US proposed package insert, the instructions were revised to address the issues observed in the study and reported during the initial marketing in Europe and the United Kingdom.

The applicant has satisfactorily addressed the issues listed in the FDA’s Complete Response Letter of October 17, 2013.

Safety

120 Day Safety Update Review

No additional safety information for the FAME studies is available.

Safety results for the FAMOUS study and Study NA-00012714 (the MAP study), an investigator-sponsored study, were submitted in Alimera’s response to the FDA’s second CRL and were based on final 36-month data for those studies. No additional information is available.

Safety Update information for the additional studies is provided in the following tables.

1) Study C-01-11-008 (FAME Extension Study)
The FAME Extension Study (Study C-01-11-008) is a 12 month, open-label, multi-center extension study of the safety and utility of the new applicator of ILUVIEN® (FA intravitreal implant) 0.19 mg (0.2 μg/day FA) and the safety of ILUVIEN in subjects with DME.

2) Safety Update for Study C-01-08-004 (the MAP-GA Study)

The MAP-GA study (Study C-01-08-004) was a single-center, randomized, single- masked, fellow eye comparison study of the effects of FA implants in subjects with geographic atrophy.

This study was terminated in October 2013.

3) Safety Update for Study C-01-08-006 (the FAVOR Study)

The FAVOR study (Study C-01-08-006) was a multicenter, randomized, double-masked study of the effects of 0.2 μg/day FA and 0.5 μg/day FA in subjects with central or branch retinal vein occlusion (CRVO or BRVO).

This study was terminated in October 2013.

<table>
<thead>
<tr>
<th>Most Common Events</th>
<th>Integrated FAME (N = 375)</th>
<th>FAMOUS (N = 393)</th>
<th>MAP-GA (N = 17)</th>
<th>FAVOR (N = 14)</th>
<th>FAME Extension (N = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>171 (45.6)</td>
<td>213 (54.2)</td>
<td>11 (55.0)</td>
<td>3 (30.0)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Cataract operation</td>
<td>188 (50.1)</td>
<td>231 (58.8)</td>
<td>13 (65.0)</td>
<td>3 (30.0)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Cataract subcapsular</td>
<td>28 (7.5)</td>
<td>24 (6.1)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>43 (11.5)</td>
<td>50 (12.7)</td>
<td>7 (35.0)</td>
<td>2 (20.0)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>23 (6.1)</td>
<td>22 (5.6)</td>
<td>1 (5.0)</td>
<td>1 (10.0)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>27 (7.2)</td>
<td>22 (5.5)</td>
<td>1 (5.0)</td>
<td>1 (10.0)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>51 (13.6)</td>
<td>65 (16.5)</td>
<td>4 (20.0)</td>
<td>2 (20.0)</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>19 (5.1)</td>
<td>16 (4.6)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Intracocular pressure increased</td>
<td>132 (35.2)</td>
<td>170 (43.3)</td>
<td>4 (20.0)</td>
<td>7 (42.0)</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Maculopathy</td>
<td>23 (6.1)</td>
<td>34 (8.7)</td>
<td>4 (20.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Myodesopsia</td>
<td>67 (17.9)</td>
<td>68 (17.3)</td>
<td>7 (35.0)</td>
<td>2 (20.0)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Posterior capsule opacification</td>
<td>32 (8.5)</td>
<td>28 (6.4)</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Trabeculectomy</td>
<td>10 (2.7)</td>
<td>22 (5.5)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>28 (7.5)</td>
<td>20 (5.1)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>39 (10.4)</td>
<td>35 (8.9)</td>
<td>0 (0.0)</td>
<td>1 (5.0)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>13 (3.5)</td>
<td>31 (7.9)</td>
<td>0 (0.0)</td>
<td>2 (11.8)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Vitrectomy</td>
<td>19 (5.1)</td>
<td>23 (5.9)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Ocular events with an incidence \( \geq 5.0\% \) in either active treatment group in the integrated FAME studies. Incidence was based on occurrence in the study eye.

### Summary of IOP- and Cataract-Related Events in the Study Eye by Treatment Group (FAME, FAMOUS, FAVOR, MAP-GA, and FAME Extension Studies, Safety Population)

<table>
<thead>
<tr>
<th>Event</th>
<th>Integrated FAME</th>
<th>FAMOUS</th>
<th>MAP-GA</th>
<th>FAVOR</th>
<th>FAME Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most Common Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>26 (6.9)</td>
<td>20 (5.1)</td>
<td>2 (10.0)</td>
<td>0 (0.0)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>41 (10.9)</td>
<td>48 (12.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

1. Ocular events with an incidence \( \geq 5.0\% \) in either active treatment group in the integrated FAME studies. Incidence was based on occurrence in the study eye.

### Post-Marketing Experience

ILUVIEN received marketing authorization in several countries in Europe in 2012 and was launched in the United Kingdom and Germany in the second quarter of 2013. The information provided in this safety update includes all data received as of January 31, 2014.

Patient exposure is estimated based on the number of units sold as of January 31, 2014. It is
assumed that patients were treated with ILUVIEN.

A total of ten (10) spontaneous adverse event reports were received. Eight (8) of these reports were drug administration error, related to product complaints and were considered non-serious (Refer to Section 7. Comment 1 E – Summary of Technical Complaints for a complete review of these issues).

Two (2) serious adverse event reports of the drug being ineffective were also reported.

**Summary Safety Statement:**

The adverse events of increased IOP and cataract formation are also evident in these additional trials. Based on all safety data collected to date, the safety profile of ILUVIEN is expected and typical of profiles observed with glucocorticoids.

8. **Advisory Committee Meeting**

No Advisory Committee Meeting has been scheduled. There are no outstanding clinical issues which are believed to benefit from an advisory committee discussion at this time.

9. **Pediatrics**

Pediatric subjects were not studied. It would be difficult to conduct a clinical study with significant numbers of subjects because diabetic macular edema is rare in the pediatric population.

This application was reviewed by the Pediatric Review Committee (PeRC) on 10/4/10. The Committee agreed with the Division that a full waiver in pediatric patients should be granted.

10. **Other Relevant Regulatory Issues**

**DSI**

A Division of Scientific Investigations (DSI) audit was requested in the original review cycle. The DSI Clinical Inspection Summary was finalized on 12/1/10.

**FINANCIAL DISCLOSURE**

Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided.

Financial disclosure forms were reviewed. There were no principal investigators with any significant proprietary interest or any significant interest in the drug product in any of the clinical studies.

**DMEPA**

The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Iluvien under IND 72,056; in a DMEPA review dated 6/15/10 there were no concerns identified, and the name was found acceptable. In a review dated 10/13/10 there were no concerns identified, and the name was found acceptable. In a review dated 8/1/14 there were no concerns identified, and the name was found acceptable.
The proprietary name Illuvien was found to be conditionally acceptable by DMEPA on 8/6/14.

DMEPA provide tray and carton labeling comments in a review dated 8/5/14. These were combined with other discipline’s comments as appropriate and sent to the applicant on 8/15/14. A teleconference was held with the applicant (DMEPA in attendance) on 8/21/14 regarding labeling.

**OPDP**

The Office of Prescription Drug Products (OPDP) revised the substantially complete labeling in a review dated 8/13/14:

**Comment [A1]:** OPDP Comment: We recommend communicating the incidence of each of these common adverse reactions. Alternatively, we recommend including a cut off incidence rate to define the "most common adverse reactions."

**OND Response:** *Section 6.1 of the package insert contains extensive information on cataract formation and intraocular pressure elevation that cannot be concisely summarized in the Highlights.***

**Comment [A2]:** OPDP Comment: Should this be a separate Warning and Precaution? There is concern that this important information may not be communicated clearly since it is the last sentence of the W&P and the 5.2 header doesn’t relate to this information. Alternatively, would it be possible to include this information in its own paragraph within this Warning and Precaution, similar to how it is presented in the Ozurdex PI? OPDP defers to DTOP.

**OND Response:** *OPDP reviewed an early draft label. The proposed PI addresses this comment.***

**Comment [A3]:** OPDP Comment: We note that Table 2 communicates that 38% and 14% of Illuvien and placebo patients, respectively, required IOP lowering medications. For consistency, we recommend revising this sentence or Table 2 to communicate the same percentage.

**OND Response:** *OPDP reviewed an early draft label. The proposed PI addresses this comment.***

**Comment [A4]:** OPDP Comment: We note that this language used in this paragraph is described here actually known? OPDP refers to the Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (February 2009). OPDP notes that other corticosteroid opthalmic labels (such as Ozurdex and the more recent Lotemax labels) do not include this language.

OPDP further notes OPDP recommends deleting. Alternatively, if DTOP believes this information is necessary for the PI, would it be possible to include a statement that this is or similar?

**OND Response:** *OPDP reviewed an early draft label. The proposed PI addresses this comment.***

**Comment [A5]:** OPDP Comment: Are these pooled results considered substantial evidence? OPDP is concerned that the pooling of data from two separate studies is misleading because the data can make the drug seem more effective (and/or less effective) than what was observed in one of the trials. For example, OPDP notes that the mean change from baseline in BCVA was 6.3 and 2.9 for Illuvien and sham, respectively, for Study 1 and 8 and -0.2 for Illuvien and sham, respectively, for Study 2. The pooling of the data suggests that the mean change in baseline is 7.1 and 1.5 for Illuvien and sham, respectively, which overstates the efficacy results observed in Study 1 Pseudophakic Subjects.

OPDP notes that the currently approved Ozurdex label includes a similar table presenting pooled data results.

If the pooling of these subgroups from the two studies is not supported by substantial evidence, we recommend deleting this table and simply presenting the results for each group for each study as it’s done in the graphs above.

**OND Response:** *OPDP reviewed an early draft label. The proposed PI addresses this comment.***

Reference ID: 3630039
Comment [A6]: OPDP Comment: We note that the Ozurdex PI includes additional counseling information regarding the potential for cataract development. We note that Iluvien is associated with an 82% incidence of cataract development. Would it be appropriate to include, “Advise patients that a cataract may occur after treatment with Iluvien? If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision,” or similar.

OND Response: *OPDP reviewed an early draft label. The proposed PI addresses this comment.*

**BIOSTATISTICS**

From the Biostatistics review dated 9/2/2014:

Efficacy of ILUVIEN (0.2µg/day) for the treatment of diabetic macular edema was demonstrated in two phase 3, three-arm, Sham-controlled studies (Study A and Study B) based on statistically significant results for the primary efficacy endpoint of the proportion of subjects with a 15 letter or more gain from baseline evaluated at Month 24. Compared to Sham, approximately 12% [95% CI: (2.6%, 21.6%)] and 13% [95% CI: (2.6%, 23.2%)] more subjects in the ILUVIEN (0.2 µg/day) arm gained 15 letters or more in best-corrected visual acuity (BCVA) at Month 24 in Study A and Study B, respectively. Note that the treatment effect was not statistically significant at Month 36 in either of the two studies; however, the observed differences were numerically in favor of the ILUVIEN (0.2 µg/day) arm.

The analysis of the mean change from baseline in BCVA at months 24 and 36, the secondary efficacy endpoint, was supportive of the results of the dichotomous primary endpoint in Study B but not in Study A. In Study B, subjects in the ILUVIEN (0.2 µg/day) arm on average gained 5 [95% CI: (1, 9)] more letters in BCVA from baseline at Month 24 compared to Sham.

In summary, based on the totality of the efficacy findings, this reviewer concludes that there is evidence to support the efficacy of ILUVIEN (0.2 µg/day) for the treatment of DME provided that the observed treatment effect is deemed clinically meaningful and outweighs the safety risks of cataract surgery and elevated IOP.

11. **Labeling**

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is recommended for approval for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure with the labeling found in the Appendix of this review (submitted by the applicant on 8/27/14).

Regarding this labeling:

1. **Table 3: Summary of Elevated Intraocular Pressure (IOP) Related Adverse Reaction**

   The Agency noted that IOP elevation ≥10 mm Hg from Baseline at any visit and ≥30 mm Hg IOP at any visit were potentially useful to clinicians because they represent clinically relevant alterations in intraocular pressure which are likely to prompt a clinician to change their management plan. Elevations ≥10 mm Hg from baseline would not occur randomly or by chance. Elevations ≥30 mm Hg IOP would be expected to be addressed by a treating physician since they also would not occur randomly or by chance and a clinician would normally evaluate the patient to determine whether they believe that the patient’s optic nerve could handle that level of IOP.
2. In the (0)(G) section of the labeling, the Agency questioned (0)(G)

3. In clinical trials of glaucoma patients before a product has been identified as being able to lower intraocular pressure, it is common to exclude the subgroup defined as “Glaucoma patients with a cup to disc ratio of greater than 0.8.” Consideration was given to revising the contraindication to patients with glaucoma who have a cup to disc ratio of greater than 0.8, and the labeling has been revised.

12. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is recommended for approval for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

RISK BENEFIT ASSESSMENT:
The recommendation for this approval is based on the risk/benefit of the drug:

1. Steroids have a Class labeling effect where it is known that steroids cause IOP elevation and cataract formation. Cataract formation is a known risk of steroid therapy and subjects who are phakic are eligible for the treatment.

2. The revised label reduces the risk of treating subjects who experience a spike in IOP elevation when treated with a steroid. Only subjects that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure will be recommended to have the treatment.

3. Only those subjects that have had previous steroid treatment for DME and did not have a clinically significant rise in intraocular pressure are recommended to receive Iluvien.

4. The benefits outweigh the risks in the indicated population (i.e. use in subjects that have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure) with the revised package insert.
Appendix

NDA 201923 Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg is recommended for approval for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure with the labeling found in this review (submitted by the applicant on 8/27/14).

Tray labeling

Carton labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
09/18/2014

WILEY A CHAMBERS
09/18/2014