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 "l" 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

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/

WILLIAM M BOYD
09/22/2014

WILEY A CHAMBERS
09/23/2014

Cross-Discipline Team Leader Review for NDA 201923

Date	September 17, 2014
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	201923
Applicant	Alimera Sciences, Inc.
Date of Submission	March 26, 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
Recommended:	Recommended for Approval

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 0.25µg/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 (aflibercept) Injection is also approved for the treatment of DME; the supplemental biologics license application was approved 7/29/2014. Ozurdex (dexamethasone intravitreal mplant) 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:

(b) (4)

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 1: Specifications for Fluocinolone Acetonide

Test	Acceptance Criteria	Analytical Method
Physical Appearance	White or practically white crystalline powder. Free of black specks or any foreign particles	CTM-200341
Identification		
(b) (4)	Compares to Standard	Current USP/NF <197K>
	Compares to Standard	Current USP/NF <201>
Identification by HPLC	Conforms	CTM-200500
Specific Rotation	Between +98° and +108°	Current USP/NF <781S>
Loss on Drying	Not more than 1.0%	Current USP/NF <731>
Assay (b) (4)	(b) (4)	CTM-200500
Related Substances		
(b) (4)	Not more than	(b) (4) CTM-200554
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	
	Not more than	

Table 1: Specifications for Fluocinolone Acetonide (Continued)

Test	Acceptance Criteria	Analytical Method
(b) (4)	Not more than (b) (4)	
	Not more than	
Any Unspecified Impurity	Not more than	
Total Impurities	Not more than	
Residual Solvents		
(b) (4)	Not more than (b) (4)	CTM-200503
	Not more than	
	Not more than	
Particle Size[a]		
Particle (b) (4) µm	Not less than (b) (4)	(b) (4)
Particle µm	Not less than	MGR051FLU011
Particle µm	Not less than	
Polymorphism		
(b) (4)	Not less than (b) (4)	X-Ray Powder Diffraction
Microbial Limits		
Total Aerobic Count	Not more than (b) (4)	Current USP/NF <61> MTM-200155
Yeast/Mold Count	Not more than	
Specific Organisms	Absence of *S. aureus*, *E. coli*, *P. aeruginosa*, *Salmonella* species	
(b) (4)		

DRUG PRODUCT:

From the applicant's original submission dated 6/30/2010:

Table 1: Composition of Iluvien

Amount per Insert	Component	Function	Quality Standard
0.19 mg	Fluocinolone Acetonide	Active Ingredient	USP, Ph. Eur.
(b) (4)	Polyvinyl Alcohol	(b) (4)	Manufacturer's specifications
	Water for Injection		USP

a Water for Injection (b) (4)

Table 2: (b) (4)

Amount per Insert	Component	Function	Quality Standard
Not Applicable[a]	Polyimide Tubing	(b) (4)	Manufacturer's specification
(b) (4)	Silicone Adhesive		Manufacturer's specification
			(b) (4)

(b) (4)

Table 3: Inserter Components

Item	Composition
Handpiece	(b) (4)
Guideshaft	
Needle	

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

Table 1: Quality Control Specifications

Test	Specification	Method
Appearance	(b) (4) light brown filled tube, no visible deformation	CTM-200341
Identification		
HPLC	Retention time of the sample compares to the retention time of the standard within (b) (4)	CTM-200501
TLC	R_f is the same as Standard	CTM-200507
Assay – Fluocinolone Acetonide	(b) (4)	CTM-200501
Related Substances		
Specified Identified and Unidentified Individual Impurity		
Release	Not more than (b) (4)	CTM-200501
Stability	Not more than	
(b) (4)		
Release	Not more than	CTM-200562
Stability	Not more than	
Unspecified Individual Impurity		
Release	Not more than (b) (4)	CTM-200501
Stability	Not more than	
Total Impurities	Not more than	
Release Rate	(b) (4) µg/day	CTM-200502

Table 1: Quality Control Specifications (Continued)

Test	Specification	Method
Endotoxin	(b) (4)	PTS-200566 MTM-200033
Sterility		(b) (4)
Release		
Stability – Container Closure Integrity	Conforms	EPS-SOP-SAS-093

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 (b) (4) µg/day for drug product *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 **Approval**.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 201923/000	**Action Goal:**	
Stamp Date:	30-JUN-2010	**District Goal:**	28-JUL-2014
Regulatory:	26-SEP-2014		
Applicant:	ALIMERA SCIENCES INC 6120 WINDWARD PKY STE 290 ALPHARETTA, GA 30005	**Brand Name:** **Estab. Name:** **Generic Name:**	FLUOCINOLONE ACETONIDE INTRAVITREAL INSE
Priority:	3	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	590	001; INSERT; FLUOCINOLONE ACETONIDE; .19MG	

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 APPLCIATION-PRIORITY (on 13-JUL-2010 by A. CUFF (HF-01) 3017964061)

FDA Contacts:				
Z. LI	Facility Reviewer			3017961798
L. QI	Prod Qual Reviewer			3017961436
S. FONG	Micro Reviewer	(HFD-003)		3017961501
N. BHANDARI	Product Quality PM			2404023915
D. WILLARD	Regulatory Project Mgr			3017960833
L. NG	Team Leader	(HFA-320)		3017961426

Overall Recommendation:					
ACCEPTABLE	on 28-JUL-2014	by T. SHARP	()	3017963208
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 22-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) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

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. CUFF (HF-01) 3017964061)

Profile: NOT ELSEWHERE CLASSIFIED **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	14-JUL-2010				CUFFA
SUBMITTED TO DO	20-JUL-2010	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	27-JUL-2010	Product Specific and GMP Inspection			CEVERLY
INSPECTION SCHEDULED	04-AUG-2010		27-AUG-2010		CEVERLY
INSPECTION PERFORMED	(b) (4)		(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 CONCURS 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; (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.					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

CARYN MCNAB, PRE-APPROVAL MANAGER

OC RECOMMENDATION	23-JUN-2011		ACCEPTABLE	INYARDA
SUBMITTED TO OC	22-MAY-2013			BHANDARIN
SUBMITTED TO DO	23-MAY-2013	GMP Inspection		PRABHAKARAR

OVERDUE FOR GMP INSPECTION. ALSO, CLARIFICATION OF PROFILE CLASS NEEDED (b) FOR INTRAVITREAL INSERT - IS THIS CORRECT?).

INSPECTION PERFORMED	(b) (4)	(b) (4)		CEVERLY
DO RECOMMENDATION	19-AUG-2013		WITHHOLD	CEVERLY

AN INSPECTION PERFORMED (b) (4) DISCLOSED THE FOLLOWING PRODUCT SPECIFIC AND GMP DEFICIENCIES.

NDA 201-923 (ILUVIEN): INADEQUATE VALIDATION AND/OR TRANSFER FOR DP RELEASE AND STABILITY METHODS, RELEASE AND STABILITY METHOD (b) (4) NO UNIFORMITY OF DOSAGE UNITS PERFORMED, NO JUSTIFICATION (b) (4) OR RELEASE TESTING, CHANGE OF RELEASE RATE FROM FINISHED PRODUCT (b) (4), NO JUSTIFICATION FOR REJECT ACTION LIMITS, NO PROCEDURE TO CREATE, CHANGE, OR CONTROL THE ILUVIEN INSERT DEFECT CHALLENGE (b) (4) OF ILUVIEN, FAILURE TO ESTABLISH RELIABILITY OF SUPPLIER'S C OF A FOR FLUOCINOLONE ACETONIDE API, POLYVINYL ALCOHOL, AND SILICONE ADHESIVE USED IN THE MANUFACTURE OF ILUVIEN, INADEQUATE QUALIFICATION (b) (4) (b) (4) NOT ALL INCLUSIVE; PLEASE SEE FDA-483 FOR COMPLETE LIST OF DEFICIENCIES. GMP: INADEQUATE VALIDATION AND/OR TRANSFER OF METHODS FOR RELEASE AND STABILITY TESTING (b) (4)

NOT ALL INCLUSIVE; PLEASE SEE FDA-483 FOR COMPLETE LIST OF DEFICIENCIES. (b) (4) RECOMMENDS WITHHOLD OF NDA 201-923 AND W/L.

CARYN MCNAB, PRE-APPROVAL MANAGER

OC RECOMMENDATION	11-OCT-2013		WITHHOLD	WILLIAMSJU
SUBMITTED TO OC	12-MAY-2014			BHANDARIN
SUBMITTED TO DO	12-MAY-2014	10-Day Letter		PHX

PLEASE UPDATE THE FINAL INSPECTION RESULT (b) (4). THE LAST INSPECTION WAS CONDCUTED (b) (4)

DO RECOMMENDATION	12-MAY-2014		WITHHOLD	CEVERLY

(b) (4) 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 PAI AND GMP PERFORMED (b) (4). CDER CONCURRENCE MEMO SUPPORTING THE DISTRICT RECOMMENDATION WAS ISSUED ON 10/14/2013. AN UTL WAS SENT TO THE FIRM. (b) (4) (SEE CMS CASE (b) (4)). THE CURRENT AC STATUS FOR PROFILE CLASS NEC APPLIES ONLY TO COMMERCIAL PRODUCTS WITH THE SAME PROFILE CLASS. NDA 201-923 REMAINS UNACCEPTABLE DUE TO PRODUCT SPECIFIC DEFICIENCIES.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

CARYN MCNAB, PRE-APPROVAL MANAGER

INSPECTION SCHEDULED	23-JUN-2014	25-JUL-2014	CEVERLY
INSPECTION PERFORMED	(b) (4)		CEVERLY
DIO RECOMMENDATION	28-JUL-2014	ACCEPTABLE	CEVERLY
PRODUCT SPECIFIC INSPECTION PERFORMED	(b) (4)	NO 483 ISSUED (b) (4) RECOMMENDS APPROVAL.	
CARYN MCNAB, PREAPPROVAL MANAGER			
OC RECOMMENDATION	28-JUL-2014	ACCEPTABLE	SHARPT
PRODUCT SPECIFIC INSPECTION PERFORMED	(b) (4)	NO 483 ISSUED (b) (4) RECOMMENDS APPROVAL.	
CARYN MCNAB, PREAPPROVAL MANAGER			

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment Comment:

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	14-JUL-2010				CUFFA
OC RECOMMENDATION	29-JUL-2010			ACCEPTABLE	INYARDA
SUBMITTED TO OC	22-MAY-2013				BHANDARIN
OC RECOMMENDATION	22-MAY-2013			ACCEPTABLE	PRABHAKARAR
FD STABILITY TESTER					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: DRUG SUBSTANCE MANUFACTURE (on 08-MAY-2014 by N. BHANDARI () 2404023815)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	14-JUL-2010				CUFFA
SUBMITTED TO DO	20-JUL-2010	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	20-JUL-2010	GMP Inspection			STOCKM
INSPECTION PERFORMED	(b) (4)		(b) (4)		EDWIN MELENDEZ

(b) (4)

The systems covered during the current inspection include: Quality, Production, Facility & Equipment, Materials Management and Laboratory. (b) (4) Deficiencies observed during the inspection resulted in a 3 item FDA-483 issued. The deficiencies cited included:

(b) (4)

Firm?s management committed to corrective actions, 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	22-MAY-2013		ACCEPTABLE	PRABHAKARAR
SUBMITTED TO DO	21-SEP-2013	GMP Inspection		WILLIAMSJU
RESUBMITTING EER SINCE RE-EVAL IS 9/23. PDUFA IS 10/17/13.				
ASSIGNED INSPECTION TO IB	24-SEP-2013	GMP Inspection		MROSE
LAST (b) INSPECTION (b) (4)				
DO RECOMMENDATION	01-OCT-2013		ACCEPTABLE	PHILPYE
(b) (4) BASED ON FILE REVIEW, (b) WAS COVERED ON MOST RECENT INSPECTION				
OC RECOMMENDATION	01-OCT-2013		ACCEPTABLE	WITTORFR
SUBMITTED TO OC	12-MAY-2014			BHANDARIN
OC RECOMMENDATION	12-MAY-2014		ACCEPTABLE	RHX

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE (b) (4)
DRUG SUBSTANCE OTHER TESTER

Establishment Comment:

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED 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

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: (b) (4), ANALYSIS OF DRUG SUBSTANCE (on 08-MAY-2014 by N. BHANDARI () 2404023815)

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

Milestone Name / Comment / OAI Submit To OC / Request to Extend Re-eval Date To / Extension Request Comment / Reason	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC	11-JUL-2011				CUFFA
SUBMITTED TO DO UNTITLED LETTER ISSUED AFTER (b) (4) INSPECTION	12-JUL-2011	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	24-JUL-2011	GMP Inspection			PHILPYE
INSPECTION PERFORMED	(b) (4)		(b) (4)		IRIVERA
INSPECTION SCHEDULED	04-NOV-2011		(b) (4)		IRIVERA
DO RECOMMENDATION	09-NOV-2011			ACCEPTABLE	PHILPYE
OC RECOMMENDATION	09-NOV-2011			ACCEPTABLE	STOCKM
SUBMITTED TO OC	22-MAY-2013				BHANDARIN
OC RECOMMENDATION OTHER TESTER (AS INDICATED IN FORM 356H) = (b) (4) ANALYSIS OF THE DRUG SUBSTANCE	23-MAY-2013			ACCEPTABLE	PRABHAKARAR
SUBMITTED TO OC	12-MAY-2014				BHANDARIN
OC RECOMMENDATION	12-MAY-2014			ACCEPTABLE	RHX

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

Establishment Comment: THIS SITE IS FOR (b) (4) THE DRUG PRODUCT (on 08-JUL-2010 by A. CUFF (HF-01) 3017964061)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name / Comment / OAI Submit To OC / Request to Extend Re-eval Date To / Extension Request Comment / Reason	Milestone Date	Request Type	Planned Completion	Decision	Creator
SUBMITTED TO OC	14-JUL-2010				CUFFA
SUBMITTED TO DO	20-JUL-2010	10-Day Letter			STOCKM
DO RECOMMENDATION THE FIRM WAS INSPECTED (b) (4) AND PROFILED ACCEPTABLE FOR (b) (4) APPROVAL. CARYN MCNAB, PAI MANAGER	27-JUL-2010			(b) (4)E	CEVERLY
OC RECOMMENDATION	28-JUL-2010			ACCEPTABLE	INYARDA
SUBMITTED TO OC	22-MAY-2013				BHANDARIN
SUBMITTED TO DO (b) (4)	23-MAY-2013	10-Day Letter			PRABHAKARAR
DO RECOMMENDATION THE FIRM WAS RECENTLY INSPECTED (b) (4) CURRENTLY ACCEPTABLE (b) (4) RECOMMENDS APPROVAL. CARYN MCNAB, PRE-APPROVAL MANAGER	29-MAY-2013			ACCEPTABLE	CEVERLY
OC RECOMMENDATION	29-MAY-2013			ACCEPTABLE	SAFAAIJAZIR
SUBMITTED TO OC	12-MAY-2014				BHANDARIN
OC RECOMMENDATION	12-MAY-2014			ACCEPTABLE	RHX

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 [redacted] (b) (4) µg/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 [redacted] (b) (4)

The applicant proposed in this March 27, 2013, resubmission that the new proposed specification for release rate be [redacted] (b) (4) µg/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 [redacted] (b) (4) is acceptable by the Agency.

Test	Acceptance Criteria	Method
Release Rate	[redacted] (b) (4) µg/day	CTM-200502

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:

[redacted] (b) (4)

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 (b) (4) units of Iluvien were used that contained the European Union instructions. Of the (b) (4) 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 1.
Common Ocular Adverse Events in the Study Eye by Treatment Group (FAME, FAMOUS, FAVOR, MAP-GA, and FAME Extension Studies, Safety Population)

	Integrated FAME		FAMOUS		MAP-GA		FAVOR		FAME Extension
Most Common Events[1]	0.2 µg/day FA (N = 375) n (%)	0.5 µg/day FA (N = 393) n (%)	0.2 µg/day FA (N = 20) n (%)	0.5 µg/day FA (N = 17) n (%)	0.2 µg/day FA (N = 10) n (%)	0.5 µg/day FA (N = 7) n (%)	0.2 µg/day FA (N = 14) n (%)	0.5 µg/day FA (N = 6) n (%)	0.2 µg/day FA (N = 120) n (%)
Cataract	171 (45.6)	213 (54.2)	11 (55.0)	4 (23.5)	3 (30.0)	2 (28.6)	2 (14.3)	4 (66.7)	12 (10.0)
Cataract operation	188 (50.1)	231 (58.8)	13 (65.0)	5 (29.4)	3 (30.0)	2 (28.6)	3 (21.4)	3 (50.0)	5 (4.2)
Cataract subcapsular	28 (7.5)	24 (6.1)	1 (5.0)	3 (17.6)	0 (0.0)	1 (14.3)	1 (7.1)	0 (0.0)	3 (2.5)
Conjunctival haemorrhage	43 (11.5)	50 (12.7)	7 (35.0)	7 (41.2)	2 (20.0)	1 (14.3)	1 (7.1)	1 (16.7)	28 (23.3)
Dry eye	23 (6.1)	22 (5.6)	1 (5.0)	2 (11.8)	1 (10.0)	1 (14.3)	1 (7.1)	1 (16.7)	5 94.2)
Eye irritation	27 (7.2)	22 (5.6)	1 (5.0)	2 (11.8)	1 (10.0)	0 (0.0)	1 (7.1)	0 (0.0)	2 (1.7)
Eye pain	51 (13.6)	65 (16.5)	4 (20.0)	2 (11.8)	2 (20.0)	0 (0.0)	3 (21.4)	1 (16.7)	11 (9.2)
Glaucoma	19 (5.1)	18 (4.6)	1 (5.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)
Intraocular pressure increased	132 (35.2)	170 (43.3)	4 (20.0)	7 (41.2)	1 (10.0)	3 (42.9)	3 (21.4)	0 (0.0)	15 (12.5)
Maculopathy	23 (6.1)	34 (8.7)	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.2)
Myodesopsia	67 (17.9)	68 (17.3)	7 (35.0)	6 (35.3)	2 (20.0)	1 (14.3)	2 (14.3)	1 (16.7)	6 (5.0)
Posterior capsule opacification	32 (8.5)	25 (6.4)	2 (10.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Trabeculectomy	10 (2.7)	22 (5.6)	1 (5.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vision blurred	28 (7.5)	20 (5.1)	1 (5.0)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)
Visual acuity reduced	39 (10.4)	35 (8.9)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	6 (5.0)
Visual impairment	13 (3.5)	31 (7.9)	0 (0.0)	2 (11.8)	2 (20.0)	1 (14.3)	0 (0.0)	0 (0.0)	2 (1.7)
Vitrectomy	19 (5.1)	23 (5.9)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Most Common Events[1]	Integrated FAME		FAMOUS		MAP-GA		FAVOR		FAME Extension
	0.2 µg/day FA (N = 375) n (%)	0.5 µg/day FA (N = 393) n (%)	0.2 µg/day FA (N = 20) n (%)	0.5 µg/day FA (N = 17) n (%)	0.2 µg/day FA (N = 10) n (%)	0.5 µg/day FA (N = 7) n (%)	0.2 µg/day FA (N = 14) n (%)	0.5 µg/day FA (N = 6) n (%)	0.2 µg/day FA (N = 120) n (%)
Vitreous detachment	26 (6.9)	20 (5.1)	2 (10.0)	1 (5.9)	0 (0.0)	1 (14.3)	1 (7.1)	0 (0.0)	3 (2.5)
Vitreous haemorrhage	41 (10.9)	48 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (6.7)

1 Ocular events with an incidence ≥ 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)

Event	Integrated FAME		FAMOUS		MAP-GA		FAVOR		FAME Extension
	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)
IOP-Related Events	**N=375**	**N = 393**	**N = 20**	**N = 17**	**N = 10**	**N = 7**	**N = 14**	**N = 6**	**N = 120**
IOP elevation considered an AE[1]	139 (37.1)	179 (45.5)	4 (20.0)	7 (41.2)	1 (10.0)	3 (42.9)	3 (21.4)	0 (0.0)	21 (17.5)
IOP elevation ≥ 12 mmHg from baseline	108 (28.8)	135 (34.4)	2 (10.0)	6 (35.3)	0 (0.0)	1 (14.3)	1 (7.1)	0 (0.0)	13 (10.8)
IOP elevation to over >25 mmHg	123 (32.8)	166 (42.2)	3(15.0)	8 (47.1)	0 (0.0)	2 (28.6)	3 (21.4)	0 (0.0)	25 (20.8)
IOP elevation to over >30 mmHg	69 (18.4)	90 (22.9)	1(5.0)	6 (35.3)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	12 (10.0)
Trabeculoplasty	5 (1.3)	10 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (0.8)
Trabeculectomy	10 (2.7)	22 (5.6)	1(5.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glaucoma surgery[2]	8 (2.1)	13 (3.3)	0 (0.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)
Vitrectomy performed for elevated IOP	1 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any surgical intervention	1 (0.5)	18 (4.8)	1 (0.5)	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)

Event	Integrated FAME		FAMOUS		MAP-GA		FAVOR		FAME Extension
	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)	0.5 µg/day FA n (%)	0.2 µg/day FA n (%)
	n (%) of Phakic Subjects/Eyes								
Cataract-Related Events	**N=235**	**N = 265**	**N = 14**	**N = 8**	**N = 4**	**N = 2**	**N = 7**	**N = 4**	**N = 33**
Cataract considered to be an AE	192 (81.7)	235 (88.7)	12 (85.7)	7 (87.5)	3 (75.0)	2 (100)	3 (42.9)	4 (100)	15 (45.5)
Cataract Extraction	188 (80.0)	231 (87.2)	13 (92.9)	5 (62.5)	3 (75.0)	2 (100)	3 (42.9)	3 (75.0)	5 (15.2)

1 Includes adverse event reports of ocular hypertension and intraocular pressure increased
2 Includes the following procedures: Ahmed valve, Baerveldt implant with stent, endocyclophotocoagulation, endocyclodestruction, laser peripheral iridotomy

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 (b) (4) 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 propriety name Iluvien 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 Iluvien 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 (b) (4) language used in this paragraph is (b) (4) Is the (b) (4) 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) (b) (4) OPDP notes that other corticosteroid ophthalmic labels (such as Ozurdex and the more recent Lotemax labels) do not include this (b) (4) language.

OPDP further notes (b) (4) therefore, (b) (4) 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 (b) (4) 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 Iluvien and sham, respectively, for Study 1 and 8 and -0.2 for Iluvien 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 Iluvien 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.*

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. (b) (4)

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 (b) (4) 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 (b) (4) section of the labeling, the Agency questioned (b) (4) [redacted]

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

(b) (4)

Carton labeling

(b) (4)

10 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/

WILLIAM M BOYD
09/18/2014

WILEY A CHAMBERS
09/18/2014