# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 201923Orig1s000

# PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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| Application number: | 201923 |
| Supporting document/s: | 49 |
| Applicant's letter date: | March 26, 2014 |
| CDER stamp date: | March 26, 2014 |
| Product: | Iluvien® (fluocinolone acetonide intravitreal insert) 0.19 mg |
| Indication: | Treatment of (b) (4) diabetic macular edema in patients (b) (4) |
| Applicant: | Alimera Sciences, Inc., Alpharetta, GA |
| Review Division: | DTOP |
| Reviewer: | Lori E. Kotch, PhD, DABT |
| Supervisor/Team Leader: | Lori E. Kotch, PhD, DABT |
| Division Director: | Renata Albrecht, MD |
| Project Manager: | Diana Willard |

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# 1 Executive Summary

On March 26 2014, Alimera Sciences Inc. provided a resubmission to NDA 201923 in response to a Complete Response Letter dated 17 October 2013. Revised draft labeling was provided.

## 1.1 Recommendations

### 1.1.1 Approvability

The application was reviewed by Drs. Conrad Chen (primary reviewer) and Wendelyn Schmidt (secondary reviewer) and submitted to DARRTs on 10-7-2010. Approval was recommended.

No further nonclinical data were submitted to the application.

### 1.1.2 Labeling –

On March 26 2014, Alimera Sciences Inc. provided a resubmission to NDA 201923 in response to a Complete Response Letter dated 17 October 2013. Revised draft labeling was provided by the Sponsor, and revisions to nonclinical sections 8 and 13 are listed below. Recommended changes to the Sponsor's labeling follow.

**Sponsor's Proposed Labeling:**

*8 USE IN SPECIFIC POPULATIONS*

*8.1 Pregnancy*

*Pregnancy Category C*

(b) (4)

*There are no adequate and well controlled studies of ILUVIEN in pregnant women. ILUVIEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.*

*8.3 Nursing Mothers*

(b) (4)

*13 NONCLINICAL TOXICOLOGY*

*13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility*

*Long-term animal studies have not been conducted to determine the carcinogenic potential or the effect on fertility of ILUVIEN.*

*Fluocinolone acetonide was not genotoxic in vitro in the Ames test (S. typhimurium and E. coli) and the mouse lymphoma TK assay, or in vivo in the mouse bone marrow micronucleus assay.*

## Reviewer Proposed Labeling:

The following labeling changes are recommended to accommodate new format within and across Divisions.

**8.1 Pregnancy**

**Pregnancy Category C**

There are no adequate and well-controlled studies of ILUVIEN in pregnant women. Adequate animal reproduction studies have not been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. ILUVIEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**8.3 Nursing Mothers**

Systemically administered corticosteroids are present in human milk and could suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of fluocinolone acetonide following intravitreal treatment with ILUVIEN is low [see Clinical Pharmacology (12.3)]. It is not known whether intravitreal treatment with ILUVIEN could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when ILUVIEN is administered to a nursing woman.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No changes to Sponsor's proposed language.

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/s/

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LORI E KOTCH
07/28/2014

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

| | |
|---|---|
| Application number: | 201-923 |
| Supporting document/s: | Electronic submission |
| Applicant's letter date: | June 28, 2010 |
| CDER stamp date: | June 28, 2010 |
| Product: | Iluvien® (fluocinolone acetonide intravitreal insert) 0.19 mg |
| Indication: | Treatment of diabetic macular edema |
| Applicant: | Alimera Sciences, Inc., Alpharetta, GA |
| Review Division: | Division of Anti-Infective and Ophthalmology Products |
| Reviewer: | Conrad H. Chen, Ph.D. |
| Supervisor/Team Leader: | Wendelyn Schmidt, Ph.D. |
| Division Director: | Wiley Chambers, MD |
| Project Manager: | Raphael Rodriguez/ Jean Dean |

*Template Version: December 7, 2009*

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# 1 Executive Summary

## 1.1 Recommendations

### 1.1.1 Approvability

Approval of NDA 201-923 is recommended.

### 1.1.2 Additional Non Clinical Recommendations

None

### 1.1.3 Labeling

The following labeling should include the information (taken from the published literature) which was also found in the Retisert labeling.

1. Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been (b) (4) .
   Fluocinolone acetonide was not genotoxic *in vitro* in the Ames test, the mouse lymphoma TK assay, or *in vivo* in the mouse bone marrow micronucleus assay.

2. Pregnancy:
   (b) (4) Pregnancy Category C.
   (b) (4)
   (b) (4) Iluvien should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### 1.2 Brief Discussion of Nonclinical Findings

The nonclinical toxicology program included a 24-month ocular toxicity and pharmacokinetics study in rabbits and a 9-month ocular toxicity study in rabbits using test article that had undergone forced degradation in an accelerated stability chamber.
There appeared to be no definable toxicity associated with the administration of 0.2 µg/day flucinolone acetonide (FA). The test article, FA, appeared to induce posterior cortical/capsular cataracts in pigmented rabbits at 0.5 and 1.0 µg/day, as indicated by the increased incidence of cataracts at these concentrations. Cataract formation is a known effect of corticosteroids. The development of these cataracts may be associated with the extended half life of FA in the lens. There was no quantifiable systemic exposure of fluocinolone acetonide following intravitreal injection of Iluvien® intravitreal inserts to male and female Dutch Belted rabbits at 0.2, 0.5 and 1.0 µg/day doses (targeted release rates). The test article FA/Medidur, after undergoing forced degradation, did not appear to induce ocular disease or systemic toxicity over a 9-month period after its placement in the vitreous of pigmented rabbits.
Fluocinolone acetonide did not show any evidence of genotoxic activity in a standard battery of tests when tested in accordance with regulatory guidelines.

## 2 Drug Information

### 2.1 Drug:

Iluvien® (fluocinolone acetonide intravitreal insert) 0.19 mg injected by a 25 gauge needle, 0.2 or 0.5 µg/day delivery rate. (Iluvien is also called FA/Medidur™)

#### 2.1.1 CAS Registry Number (Optional)

67-73-2

#### 2.1.2 Generic Name

Fluocinolone acetonide (FA)

#### 2.1.3 Code Name

ASI-001 A (0.5 µg/day) and ASI-001 B (0.2 µg/day)

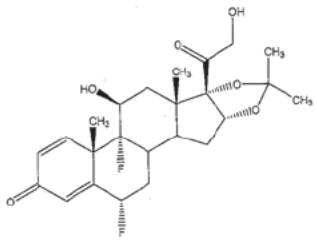
#### 2.1.4 Chemical Name

(6α,11β, 16α)-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis-(oxy)]-pregna-1,4-diene-3,20-dione

### 2.1.5 Molecular Formula/Molecular Weight

$C_{24}H_{30}F_2O_6$/452.49

### 2.1.6 Structure



### 2.1.7 Pharmacologic class

Corticosteroid

## 2.2 Relevant IND/s, NDA/s, and DMF/s

IND 72056

## 2.3 Clinical Formulation

### 2.3.1 Drug Formulation

Iluvien® (Fluocinolone Acetonide Intravitreal Insert 0.19 mg) is a sterile sustained release drug delivery system that is designed to release submicrogram levels of fluocinolone acetonide (FA) into the ocular vitreous chamber. Iluvien is manufactured by mixing FA with (b) (4)% polyvinyl alcohol (PVA) (b) (4)

### 2.3.2 Comments on Novel Excipients

Polyvinyl alcohols (PVA) are synthetic polymers used since the early 1930s in a wide range of industrial, commercial, medical and food applications including resins, lacquers, surgical threads and food contact applications. Orally administered PVA is relatively harmless, with the $LD_{50}$ in the range of 15-20 g/kg. PVA has been used at up to (b) (4)% in the ophthalmic suspension/drop and at (b) (4) mg in the intravitreal implant (FDA approved drug list). The content of PVA in 0.19 mg Iluvien is (b) (4) mg.

Polyimide tubing is used in Iluvien [redacted] (b) (4) [redacted] According to the information supplied by the sponsor, polyimide tubing meets USP Class VI Biocompatibility requirements. The studies conducted included: acute toxicity (USP), intracutaneous toxicity (USP), and paravertebral muscle implantation test (USP). The results were insignificant. One example of an intraocular lens (IOL) with a polyimide haptic (loop and hinge) is the Crystalens™. The preclinical studies on this device were consistent with the FDA draft guidance document dated October 14, 1999 for testing intraocular lenses. The Crystalens IOL has been marketed worldwide. The Crystalens has not been withdrawn from any market for reasons relating to safety and effectiveness of the device. The information is used as supportive safety information for ocular use of polyimide tubing.

The chemist reviewer of this NDA has addressed concerns regarding the biocompatibility studies in the submission. She requested pharmacology/toxicology comments for the biocompatibility studies. She mentioned that the device components of the submission are being reviewed by the CDRH.

The sponsor conducted biocompatibility studies with extracts of stainless steel needles using mouse fibroblast cells, guinea pig maximization sensitization test, and rabbit intraocular irritation test according to the requirements for medical device. The results from these studies were negative. I have expressed my opinion that these results will be considered as supportive information from the pharmacology/toxicology perspective and the product safety will be evaluated from the repeat dose animal toxicity studies.

### 2.3.3 Comments on Impurities/Degradants of Concern

The test article FA/Medidur, after undergoing forced degradation, did not appear to induce ocular disease or systemic toxicity over a 9-month period after its placement in the vitreous of pigmented rabbits. FA/Medidur test articles were placed in the 40°C/75% RH chamber for 6 months to generate exaggerated levels of degradation products in order to support the toxicity study objective. The total impurity level was [redacted] (b) (4) % (w/w %), while the highest single impurity, the known degradant product [redacted] (b) (4) was [redacted] (b) (4) % (w/w %).

## 2.4 Proposed Clinical Population and Dosing Regimen

Iluvien, a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA) has been developed for the treatment of diabetic macular edema (DME). It has been studied in 2 doses based on the initial release rate, 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 initial release rate of FA is stated as 0.25 µg/day in the labeling.

## 2.5 Regulatory Background

Iluvien has been studied under IND 72056.

During a communication from the FDA to sponsor on 02/03/10, FDA requested the human PK data be submitted for the evaluation of carcinogenicity waiver.
Response by the sponsor: Fluocinolone Acetonide (FA) was administered for up to 14 months to one eye of human subject in the form of intravitreal inserts releasing 0.5 or 0.2 µg FA per day. Plasma and aqueous humor concentrations of FA were determined. All FA plasma concentrations were below the lower limit of quantitation (LLOQ) of the assay (0.2 ng/mL) and therefore no pharmacokinetic (PK) analysis was performed.
Conclusion: Since human systemic exposure to FA after Iluvien is below LLOQ, the waiver of carcinogenicity study is granted.

There have been two different suppliers/manufacturers for drug products during the development. Therefore, in the same communication with sponsor, the FDA requested that the pivotal 24-month rabbit ocular study be conducted with the insert targeted for development and marketing. The sponsor was also requested to document any differences in the composition of the tested vs. the proposed clinical formulations.
Response by the sponsor: The Iluvien insert for the intended market product contains 0.19 mg of FA. There is a slight difference in the total FA content between the product used in the preclinical and clinical studies and the product to be marketed, i.e., the FA content of the product manufactured at pSivida averaged (b) (4) mg. However, the formulation used (b) (4) remained the same (b) (4) for the preclinical/clinical studies and the product to be marketed. FA is released from the polyimide tube at sub-microgram levels (b) (4)
Conclusion: The explanation by sponsor seems acceptable. If there is no objection from other disciplines, no further issue will be addressed on this subject.

# 3 Studies Submitted

## 3.1 Studies Reviewed

1. A 24-Month Toxicity Study of FA/Medidur™ (Fluocinolone Acetonide Controlled Release System) Administered Via Intravitreal Injection to Pigmented Rabbits (Study JOK00002)
2. A 9-Month Ocular Toxicity Study of Intravitreal Administered FA/Medidur™ (Fluocinolone Acetonide Sustained Release Insert to Pigmented Rabbits Following a Forced Degradation of the Test Article (Study JOK00001)

3. Fluocinolone Acetonide Bacterial Mutation Test (Study 961864)
4. Fluocinolone Acetonide Mammalian Cell Mutation Test (Study 962441)
5. Fluocinolone Acetonide Mouse Micronucleus Test (Study 961866)

### 3.2 Studies Not Reviewed

Literature References

### 3.3 Previous Reviews Referenced

IND 72056

# 4 Pharmacology

Fluocinolone acetonide (FA) is a synthetic corticosteroid with established clinical use to suppress inflammatory changes at various sites in the body. Topical formulations of fluocinolone acetonide are marketed in the US for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

The efficacy of FA in the intravitreal implant has been shown in rabbit model of tuberculin antigen induced uveitis. In addition, there are many published articles reporting the efficacy of corticosteroids in animal models of uveitis.

Retisert® (fluocinolone acetonide) 0.59 mg intravitreal implant, NDA 21-737, was approved on April 8, 2005. Retisert is administered by surgical implantation. Iluvien, 0.19 mg fluocinolone acetonide insert will be administered by intravitreal injection using a new delivery device.

Srivastava et al (2005) studied inserts of design similar to Iluvien delivering 0.6 (n=11) or 1.0 µg/day (n=9) in the rabbit uveitis model. Sustained-release FA inserts were placed into the vitreous of the right eyes of NZW rabbits through a 25 gauge needle 7 days after a subcutaneous injection of tuberculin antigen. Control animals (N=9) received empty inserts. Uveitis was then induced with an intravitreal injection of tuberculin antigen. Masked observers graded anterior chamber flare, cell and vitreous opacity on days 1–7, 10, and 14 after uveitis induction. Enucleated eyes and recovered inserts were used to confirm drug release rates and vitreous drug concentrations.
The test product was inserted into the vitreous cavity without complications. By clinical criteria, treated eyes were less inflamed than untreated eyes. Both dose levels significantly reduced vitreous opacity compared to controls ($p<0.04$). There was a significant reduction in anterior chamber flare ($p=0.03$) and vitreous opacity ($p<0.01$) among the 3 groups with more inflammation suppressed at the higher dose level.
(Srivastava, S., Mruthunjaya, P., Wiser, J., Peairs, J., Stinnett, S., Jaffe, G., 2005. Intravitreal sustained–release fluocinolone acetonide device to treat severe experimental uveitis. *Invest. Ophthalmol. Vis. Sci.*, 46, E-Abstract, 3536.)

# 5 Pharmacokinetics/ADME/Toxicokinetics

The Iluvien® intravitreal insert is a tiny hollow cylinder (3.5 mm x 0.37 mm) containing fluocinolone acetonide (FA) which is inserted into the vitreous by injection through a 25-gauge extra-thin walled needle. The drug delivery system releases submicrogram levels of FA into the vitreous.
The sustained-release intravitreal inserts, referred to as ASI-001B and ASI-001A, FA/Medidur™, or by the brand name Iluvien, each contained 0.19 mg of FA as the active ingredient, releasing at a target initial rate of 0.2 or 0.5 µg/day, respectively. Inactive ingredients are polyvinyl alcohol (PVA) and water for injection. The components of the delivery system (b) (4) The 0.2 µg/day version has a (b) (4)

The insert is injected through the pars plana into the vitreous using a modified 25-gauge needle that controls the injection depth. The polyimide tube is impermeable to FA, while the cured PVA coated ends of the tube act as diffusion ports allowing the drug to be released.

A pharmacokinetic satellite study of the low (0.2 µg/day) and high (0.5 µg/day) doses was performed as a part of study JOK00002, A 24-Month Toxicity Study of FA/Medidur™ to characterize the plasma and ocular tissue levels of FA. This study was performed according to GLP standards. There was no quantifiable systemic exposure of fluocinolone acetonide following intravitreal injection of Iluvien® intravitreal inserts to male and female Dutch Belted rabbits at 0.2, 0.5 and 1.0 µg/day doses (targeted release rates). The limit of quantitation of FA in the rabbit plasma was 100-200 pg/mL. The ocular concentrations declined very gradually following the first dose and then increased with the second dose at month 12 for the mid and high dose levels. The elimination of FA from the ocular tissues was very slow with elimination half-lives generally exceeding 2000 hours, and was not apparently tissue or dose dependent. The estimated half-life of FA was considered the result of the controlled release of FA from the delivery system. The exposure of FA was generally highest in the choroid and pigmented epithelium followed by the lens or retina, the iris/ciliary body, the vitreous humor or cornea. The ocular exposure of FA in the aqueous humor was minimal at all dose levels in rabbits. The local ocular tissue exposure increased with the dose, though no clear evidence of dose proportionality was indicated. There was no evidence of gender differences in ocular exposure of FA at any dose level. The observed exposure profiles are consistent with the mode of administration of FA.

**Table 1: Pharmacokinetic Exposure Parameters of Fluocinolone Acetonide (FA) in Dutch Belted Rabbit Ocular Tissues Following Intravitreal Injection of FA/Medidur™**

**Males**

| Group No. | Dose Level (µg/day) | Animal No. | $C_{max}$ (ng/g) | $AUC_{(0\text{-}last)}$ (ng•h/g) | $AUC_{(0\text{-}\infty)}$ (ng•h/g) | AUC% (tlast-∞) | $C_{max}$/ Dose | $AUC_{(0\text{-}last)}$/ Dose |
|---|---|---|---|---|---|---|---|---|
| 3 | 0.2 | Aqueous Humor | a | a | a | a | - | - |
| | | Vitreous Humor | 1.49 | 4696 | 4777 | 1.68 | 7.43 | 23482 |
| | | Lens | 4.86 | 57202 | b | b | 24.3 | 286010 |
| | | Cornea | 1.43 | 4710 | b | b | 7.14 | 23549 |
| | | Retina | 11.9 | 36020 | b | b | 59.3 | 180098 |
| | | Choroid and Pigmented Epithelium | 75.9 | 182848 | 195791 | 6.61 | 379 | 914238 |
| | | Iris/Ciliary Body | 41.8 | 120408 | 123425 | 2.44 | 209 | 602042 |
| 4 | 0.5 | Aqueous Humor | a | a | a | a | - | - |
| | | Vitreous Humor | 6.54 | 39824 | 42667 | 6.66 | 13.1 | 79647 |
| | | Lens | 36.0 | 306147 | c | 27.3 | 71.9 | 612294 |
| | | Cornea | 8.13 | 26438 | c | 37.0 | 16.3 | 52876 |
| | | Retina | 43.0 | 209878 | b | b | 86.0 | 419755 |
| | | Choroid and Pigmented Epithelium | 84.7 | 615485 | 684279 | 10.1 | 169 | 1230970 |
| | | Iris/Ciliary Body | 42.4 | 215204 | 236420 | 8.97 | 84.7 | 430409 |
| 5 | 1.0 | Aqueous Humor | a | a | a | a | - | - |
| | | Vitreous Humor | 59.3 | 69133 | 74898 | 7.70 | 59.3 | 69133 |
| | | Lens | 100 | 831241 | b | b | 100 | 831241 |
| | | Cornea | 7.67 | 41869 | c | 50.0 | 7.67 | 41869 |
| | | Retina | 144 | 454825 | 475049 | 4.26 | 144 | 454825 |
| | | Choroid and Pigmented Epithelium | 145 | 1211731 | 1334543 | 9.20 | 145 | 1211731 |
| | | Iris/Ciliary Body | 88.7 | 424327 | 480216 | 11.6 | 88.7 | 424327 |

a PK parameters not estimated due to samples being BLQ.

b No reportable results as the terminal phase could not be identified.

c Values are not reported because the $AUC_{(0\text{-}\infty)}$ was extrapolated by more than 20% or $R^2$ was <0.8.

- Not calculated.

**Table 2: Pharmacokinetic Exposure Parameters of Fluocinolone Acetonide (FA) in Dutch Belted Rabbit Ocular Tissues Following Intravitreal Injection of FA/Medidur™**

**Females**

| Group No. | Dose Level (µg/day) | Animal No. | $C_{max}$ (ng/g) | $AUC_{(0\text{-}dlast)}$ (ng•h/g) | $AUC_{(0\text{-}\infty)}$ (ng•h/g) | AUC% (tlast-∞) | $C_{max}$/ Dose | $AUC_{(0\text{-}tlast)}$/ Dose |
|---|---|---|---|---|---|---|---|---|
| 3 | 0.2 | Aqueous Humor | 0.197 | d | b | b | 0.985 | - |
| | | Vitreous Humor | 1.21 | 3319 | 3840 | 13.6 | 6.06 | 16597 |
| | | Lens | 33.4 | 62981 | 72219 | 12.8 | 167 | 314906 |
| | | Cornea | 1.67 | 1417 | b | b | 8.37 | 7085 |
| | | Retina | 12.6 | 9327 | c | 79.7 | 63.1 | 46633 |
| | | Choroid and Pigmented Epithelium | 52.0 | 123798 | c | 18.7 | 260 | 618988 |
| | | Iris/Ciliary Body | 19.3 | 76067 | 79456 | 4.27 | 96.4 | 380335 |
| 4 | 0.5 | Aqueous Humor | a | a | a | a | - | - |
| | | Vitreous Humor | 10.5 | 51068 | 52079 | 1.94 | 21.0 | 102137 |
| | | Lens | 68.8 | 574162 | b | b | 138 | 1148324 |
| | | Cornea | 7.25 | 40041 | b | b | 14.5 | 80083 |
| | | Retina | 92.3 | 428761 | b | b | 185 | 857522 |
| | | Choroid and Pigmented Epithelium | 93.9 | 677477 | 721815 | 6.14 | 188 | 1354954 |
| | | Iris/Ciliary Body | 45.4 | 209552 | 219496 | 4.53 | 90.7 | 419103 |
| 5 | 1.0 | Aqueous Humor | 0.377 | d | b | b | 0.377 | - |
| | | Vitreous Humor | 27.4 | 90143 | c | 4.03 | 27.4 | 90143 |
| | | Lens | 207 | 632130 | c | 36.7 | 207 | 632130 |
| | | Cornea | 14.9 | 68171 | 70249 | 2.96 | 14.9 | 68171 |
| | | Retina | 202 | 638958 | c | 3.70 | 202 | 638958 |
| | | Choroid and Pigmented Epithelium | 236 | 1823285 | 1923426 | 5.21 | 236 | 1823285 |
| | | Iris/Ciliary Body | 138 | 366531 | 439440 | 16.6 | 138 | 366531 |

a PK parameters not estimated due to samples being BLQ.
b No reportable results as the terminal phase could not be identified.
c Values are not reported because the $AUC_{(0\text{-}\infty)}$ was extrapolated by more than 20% or $R^2$ was <0.8.
d Value not considered reportable because the number of quantifiable plasma concentration time-points was less than 3.
- Not calculated.

# 6 General Toxicology

## 6.1 Single-Dose Toxicity

No single dose (acute) toxicity studies have been conducted with Iluvien by the sponsor.

## 6.2 Repeat-Dose Toxicity

Study title: A 24-month toxicity study of FA/Medidur™ (fluocinolone acetonide controlled release system) administered via intravitreal injection to pigmented rabbits

| | |
|---|---|
| Study no.: | Study No. JOK00002 |
| Study report location: | |
| Conducting laboratory and location: | [redacted] (b) (4) |
| Date of study initiation: | February 19, 2007 |
| GLP compliance: | Yes |
| QA statement: | Yes |
| Drug, lot #, and % purity: | Notebook #311-23 (Batch #DE-07-0017 for Group 4, Batch #DE-07-0018 for Group 5) |

### Key Study Findings

There appeared to be no definable toxicity associated with the administration of 0.2 µg/day FA. The test article, FA, appeared to induce posterior cortical/capsular cataracts in pigmented rabbits at 0.5 and 1.0 µg/day, as indicated by the increased incidence of cataracts at these concentrations. The development of these cataracts may be associated with the extended t1/2 of FA in the lens. Lens deformity upon gross examination was recorded only in one animal each out of 8 animals receiving 0.5 or 1.0 µg/day.

There was no quantifiable systemic exposure of fluocinolone acetonide following intravitreal injection of Iluvien® intravitreal inserts to male and female Dutch Belted rabbits at 0.2, 0.5 and 1.0 µg/day doses (targeted release rates). The ocular concentrations declined very gradually following the first dose and then increased with the second dose at month 12 for the mid and high dose levels. The elimination of FA from the ocular tissues was very slow with elimination half-lives generally exceeding 2000 hours, and was not apparently tissue or dose dependent. The estimated half-life of FA was considered the result of the controlled release of FA from the delivery system. The exposure of FA was generally highest in the choroid and pigmented epithelium followed by the lens or retina, the iris/ciliary body, the vitreous humor or cornea. The ocular exposure of FA in the aqueous humor was minimal at all dose levels in rabbits. The local ocular tissue exposure increased with the dose, though no clear evidence of dose proportionality was indicated. There was no evidence of gender differences in

ocular exposure of FA at any dose level. The observed exposure profiles are consistent with the mode of administration of FA.

Methods

Doses:

Table 3: 24-Month Ocular Toxicity Study in Pigmented Rabbits (JOK00002)

| Group Number | Number of Main Study Animals | | Number of Pharmacokinetic Animals | | Test Article | Number of Devices | Daily Dose of Fluocinolone Acetonide (FA) (µg/day)[1] |
|---|---|---|---|---|---|---|---|
| | Males | Females | Males | Females | | | |
| 1 | 4 | 4 | | | Sham control | Sham control[2] | 0 |
| 2 | 4 | 4 | | | Placebo | 1 (Placebo)[2] | 0 |
| 3 | 4 | 4 | 10 | 10 | FA/Medidur™ | 2 | 0.2 |
| 4 | 4 | 4 | 10 | 10 | FA/Medidur™ | 2[3] | 0.5 |
| 5 | 4 | 4 | 10 | 10 | FA/Medidur™ | 4[4] | 1.0 |

1 Based on the nominal release rate

2 Sham injections and placebo injections performed in the right and left eyes on Study Day 1

3 One device in the right and left eyes on Study Day 1, and another during Week 52

4 Two devices in the right and left eyes on Study Day 1, and two during Week 52

Frequency of dosing: First injection on Day 1 and second injection on Week 52

Route of administration: Intravitreal injection in pre-filled syringes

Dose volume: One or two devices per injection per eye

Formulation/Vehicle: Intravitreal insert (placebo, 0.2, 0.5 and 1.0 µg/day release rate)

Species/Strain: Dutch Belted rabbits

Number/Sex/Group: 4/sex/group

Age: 5 to 6 months old

Weight: 2.2 to 2.6 kg for male, 2.0 to 2.5 kg for female

Satellite groups: 10/sex/group for pharmacokinetics

Unique study design: The main study animals were euthanized and necropsied on Study Day 729, and the pharmacokinetic animals (1/sex/group on Study Days 2 and 8 and at Weeks 5, 8, 13, 26, 39, 52, 78, and 104).

Deviation from study protocol: Corneal tissue analysis by (b) (4) was not performed under GLP. Analysis of the retrieved implants and Certificates of Analysis by pSvida, Inc. were not performed under GLP.

## Observations and Results

There were no test article-related gross findings with the possible exception of one animal each in Groups 4 and 5; these animals had a finding of lens deformity (rough surface area). There were no apparent abnormal test article-related changes to the morphology of the eye.

Histopathologic examination revealed focal retinal scarring, which was seen more frequently in the area of the injection site in the eyes of the rabbits treated with inserts than in rabbits subjected only to the sham injection. This effect was more apparent in the rabbits from the groups which received multiple inserts, and is probably related to the injection procedure. No changes were detected in the lenses to indicate any

cataractogenic activity, and there was no apparent retinal or optic nerve damage suggestive of glaucoma. Cataracts were observed in Groups 4 and 5 on ophthalmologic examination, but similar findings were not noted upon histological examination.
A plausible explanation given by the sponsor for the discrepancy between the evaluations may be secondary effects of tissue fixation, resulting in the masking of cataract detection using hematoxylin and eosin staining.

## Toxicokinetics

Quantifiable FA concentrations were not observed at any dose level in the plasma of rabbits administered FA/Medidur (quantitation limit of 200 pg/mL); therefore, systemic pharmacokinetics of FA could not be assessed.
In general, FA exposure was generally highest in the choroid and pigmented epithelium, followed by the lens or retina, the iris/ciliary body, the vitreous humor or cornea. With the exception of one eye of one animal (at 0.2 µg/day), FA was undetectable in aqueous humor up to 0.5 µg/day, and the exposure of FA in aqueous humor was minimal at 1.0 µg/day. The local exposure of FA generally increased with the dose in both male and female rabbits; however, there was no clear evidence of dose proportionality in the ocular exposure of FA in the dose range of 0.2 to 1.0 µg/day.
Overall, elimination of FA from the ocular tissues was very slow without apparent tissue or dose dependence, and was considered a reflection of the controlled (continuous) release of FA from the FA/Medidur delivery system. Near-steady vitreous humor, lens, cornea, retina, choroid and pigmented epithelium, and iris/ciliary body tissue concentrations of FA were maintained following intravitreal administration of FA/Medidur. The left and right eye mean tissue concentrations declined very gradually with elimination half-lives (t1/2) generally exceeding 2000 hours.

For results see Table 1 and 2 under **5 Pharmacokinetics/ADME/Toxicokinetics.**

Study title: A 9-Month Ocular Toxicity Study of Intravitreal Administered FA/Medidur™ (Fluocinolone Acetonide Sustained Release Insert to Pigmented Rabbits Following a Forced Degradation of the Test Article

| | |
|---|---|
| Study no.: | Study JOK00001 |
| Study report location: | |
| Conducting laboratory and location: | (b) (4) |
| Date of study initiation: | July 30, 2007 |
| GLP compliance: | Yes |
| QA statement: | Yes |
| Drug, lot #, and % purity: | Notebook 311-6 |

**Key Study Findings:**

The test article FA/Medidur, after undergoing forced degradation, did not appear to induce ocular disease or systemic toxicity over a 9-month period after its placement in the vitreous of pigmented rabbits.

Doses: FA/Medidur test articles were placed in the 40°C/75% RH chamber for 6 months to generate exaggerated levels of degradation products in order to support the toxicity study objective. The total impurity level was (b) (4) % (w/w%), while the highest single impurity, the known degradant product (b) (4), was (b) (4) % (w/w%).

| Group Number | Number of Main Study Animals | | Test Article | Number of Devices/Eye | Daily Dose of Fluocinolone Acetonide (µg/day/eye)[a] |
|---|---|---|---|---|---|
| | Males | Females | | | |
| 1 | 4 | 4 | Sham control | Sham control | 0 |
| 2 | 4 | 4 | Placebo | 2 (Placebo) | 0 |
| 3 | 7 | 7 | FA/Medidur™ | 2 | 1.0 |

[a] Based on the nominal release rate

Frequency of dosing: Sham injections, placebo, and 1.0 µg/day (two devices) test article were administered once to the right eye of each animal in Groups 1, 2, and 3, respectively.

Route of administration: Intravitreal injection in pre-filled syringes

Dose volume: Two inserts designed to release 0.5 µg/day for a total release rate of 1.0 µg/day were used.

Formulation/Vehicle: Test article syringes containing the exaggerated dose (two inserts designed to release 0.5 µg/day for a total release rate of 1.0 µg/day) and syringes containing the placebo device (no FA content) were supplied. Additionally, sham injectors were provided for dosing Group 1.

Species/Strain: Dutch Belted rabbits

Number/Sex/Group: 4-7/sex/group

Age: 6 months old

Weight: The males weighed 2.3 to 2.6 kilograms, and the females weighed 2.2 to 2.5 kilograms.

Satellite groups: None

Unique study design: The test articles were stored for 6 months under the accelerated degradation condition before the test. The terminal pathology was conducted on Days 91 and 274.

Deviation from study protocol: Not reported.

**Observations and Results**

At the completion of the 6-month storage under accelerated conditions, the FA/Medidur test articles met the specifications for assay, impurities, and release rate. The total impurity level was [redacted] % (w/w%), while the highest single impurity, the known degradant product [redacted], was [redacted] % (w/w%).
There were no findings that were definitively ascribed to administration of the FA/Medidur test article. Posterior lens opacity was observed on ophthalmic examination in one rabbit in the sham control group and in two rabbits in the FA/Medidur group, and was likely a result of physical contact of the insert with the posterior lens capsule, rather than a direct result of the FA test article. Histological findings that were present in the eyes of some animals administered FA/Medidur, but not in those receiving sham control or placebo, and that may have been related to the FA test article were restricted to focal degenerative lesions affecting fibers in the posterior polar and posterior cortical regions of the lens. It appears that the lens fiber degeneration (cataract development) in the posterior subcapsular region of the lens is a recognized effect of corticosteroids.
The test article, FA/Medidur™, following a forced degradation, does not appear to induce ocular disease or systemic toxicity when placed in the vitreous of pigmented rabbits.

# 7 Genetic Toxicology

## 7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: : Fluocinolone acetonide Bacterial Mutation Test
Study no.: Study No. 961864
Study report location:
Conducting laboratory and location: [redacted]
Date of study initiation: March 24, 2009
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: 2151NM1

**Key Study Findings**

No substantial increases in the revertant colony counts were obtained with any strain following exposure to the test article in either the plate incorporation or pre-incubation assay in the absence or presence of S9 mix. It is concluded that Fluocinolone acetonide did not show any evidence of genotoxic activity in this *in vitro* mutagenicity assay when tested in accordance with regulatory guidelines.

Methods

| | |
|---|---|
| Strains: | *S. typhimurium* TA1535 *his*G46 *rfa ΔuvrB*<br>*S. typhimurium* TA1537 *his*C3076 *rfa ΔuvrB*<br>*S. typhimurium* TA98 *his*D3052 *rfa ΔuvrB* pKM101<br>*S. typhimurium* TA100 *his*G46 *rfa ΔuvrB* pKM101<br>*E. coli* WP2 *trp uvrA* |
| Concentrations in definitive study: | From 1.58 µg/plate up to 5000 µg/plate |
| Basis of concentration selection: | 5000 µg/plate is the standard limit dose recommended by regulatory guidelines (ICH). |
| Negative control: | Vehicle (DMSO) |
| Positive control: | Sodium azide (NaAz), 9 Aminoacridine (9AC), 2-Nitrofluorene (2NF), 4-Nitroquinoline N-oxide (NQO), 2-Aminoanthracene (2AA), Benzo[a]pyrene (BaP) |
| Formulation/Vehicle: | FA in Dimethyl Sulfoxide (DMSO) |
| Incubation & sampling time: | 48 to 72 hours |

**Study Validity**

Appropriate positive control compounds (with S9 mix where required) induced increases in revertant colony numbers to at least twice the concurrent vehicle control levels with the appropriate bacterial strain (1.5× for strain TA100), confirming sensitivity of the test system and activity of the S9 mix.

**Results**

The mean revertant colony counts for the vehicle controls were close to or within the laboratory historical control range. Appropriate positive control compounds (with S9 mix where required) induced increases in revertant colony numbers to at least twice the concurrent vehicle control levels with the appropriate bacterial strain (1.5× for strain TA100), confirming sensitivity of the test system and activity of the S9 mix.
No substantial increases in revertant colony numbers were obtained with any of the tester strains following exposure to Fluocinolone acetonide at any dose level in either the plate incorporation or pre-incubation assay in the presence or absence of S9 mix.
No visible thinning of the background lawn of non-revertant bacteria or substantial reduction in revertant colony counts was obtained following exposure to Fluocinolone acetonide, indicating that the test article was non-toxic to the bacteria at the levels tested. Precipitation was observed at the highest dose level tested and at 1581 µg/plate in the pre-incubation assay in presence of S9 mix.

## 7.2 *In Vitro* Chromosomal Aberration Assays in Mammalian Cells

Study title Fluocinolone Acetonide Mammalian Cell Mutation Test

| | |
|---|---|
| Study no.: | Study No. 962441 |
| Study report location: | |
| Conducting laboratory and location: | (b) (4) |
| Date of study initiation: | March 19, 2009 |
| GLP compliance: | Yes |
| QA statement: | Yes |
| Drug, lot #, and % purity: | 2151NM1 |

## Key Study Findings

No substantial increases in mutation frequency were observed after treatment of cells with Fluocinolone acetonide at dose levels up to a concentration that was not completely soluble in the final culture medium or the limit of toxicity, as appropriate in each treatment regime. It is concluded that Fluocinolone acetonide did not show any evidence of genotoxicity in this *in vitro* test when tested in accordance with regulatory guidelines.

Methods

| | |
|---|---|
| Cell line: | Mouse lymphoma L5178Y TK+/- (clone 3.7.2C) cells |
| Concentrations in definitive study: | From 4.69 up to 1200 µg/plate final concentration |
| Basis of concentration selection: | The dose levels for the main test were based on the results of the preliminary toxicity test. Where there was toxicity, dose concentrations were selected to cover an estimated range of toxicity from approximately 10-20% to approximately 80-90% RTG (relative total growth). |
| Negative control: | Vehicle (DMSO) |
| Positive control: | 4-Nitroquinoline N-oxide (NQO), Benzo(a)pyrene (BaP) |
| Formulation/Vehicle: | FA in DMSO |
| Incubation & sampling time: | In the main test, mouse lymphoma L5178Y TK+/- cells were incubated with the vehicle, test article or positive control for 3 hours (with and without S9 metabolic activation) or 24 hours (without S9 only). Following a subsequent 48 hour growth recovery period, the cells were transferred to selective medium (in microwell plates) which allowed only the growth of mutant cells into colonies. |

## Study Validity

A preliminary toxicity test was used to determine dose levels for the main test. Responses to the positive controls confirmed the sensitivity of the assay and the activity of the S9 mix.

## Results

**Table 1 Summary of Results**

| Treatment | Final Conc. (µg/mL) | % PE Viability | % RTG | Mutant Frequency SC | Mutant Frequency LC | Mutant Frequency Total | Dose Response |
|---|---|---|---|---|---|---|---|
| *3 hour treatment in the absence of S9* | | | | | | | |
| DMSO | - | 83 | 100 | 40 | 131 | 171 | |
| Fluocinolone acetonide | 75.0 | 69 | 81 | 31 | 116 | 148 | NR |
| | 150 | 70 | 75 | 34 | 201 | 235 | |
| | 300 ppt | 58 | 59 | 34 | 101 | 135 | |
| | 600 ppt | 53 | 54 | 29 | 118 | 147 | |
| NQO | 0.40 | 61 | 49 | 228 | 313 | 540 | + |
| *3 hour treatment in the presence of S9* | | | | | | | |
| DMSO | - | 79 | 100 | 35 | 67 | 102 | |
| Fluocinolone acetonide | 75.0 | 77 | 88 | 58 | 103 | 161 | NR |
| | 150 | 67 | 74 | 43 | 82 | 125 | |
| | 300 | 70 | 70 | 37 | 73 | 111 | |
| | 600 ppt | 72 | 65 | 21 | 43 | 65 | |
| BaP | 1.2 | 56 | 48 | 354 | 154 | 508 | + |
| *24 hour treatment in the absence of S9* | | | | | | | |
| DMSO | - | 69 | 100 | 22 | 111 | 133 | |
| Fluocinolone acetonide | 18.8 | 80 | 101 | 17 | 127 | 144 | NR |
| | 37.5 | 59 | 63 | 37 | 108 | 144 | |
| | 75.0 | 59 | 45 | 27 | 142 | 170 | |
| | 86.5 | 38 | 13 | 33 | 202 | 235 | |
| NQO | 0.14 | 48 | 19 | 233 | 406 | 638 | + |

NR Negative response, *i.e.* no substantial increase (equal to or higher than 126 mutants per $10^6$ viable cells) in the mutation frequency over the concurrent vehicle control

\+ Positive response, i.e. substantial increase in the mutation frequency over the concurrent vehicle control

ppt Precipitate observed in the medium at the end of treatment

See Section 8 (Evaluation and interpretation of results) for definitions of PE, RTG, SC and LC

No substantial increases in mutation frequency were observed after treatment of cells with Fluocinolone acetonide at dose levels up to a concentration that was not completely soluble in the final culture medium or the limit of toxicity, as appropriate in each treatment regime. It is concluded that Fluocinolone acetonide did not show any evidence of genotoxicity in this *in vitro* test when tested in accordance with regulatory guidelines.

## 7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Fluocinolone Acetonide Mouse Micronucleus Test

| | |
|---|---|
| Study no.: | Study No. 961866 |
| Study report location: | |
| Conducting laboratory and location: | [redacted] (b) (4) |
| Date of study initiation: | March 25, 2009 |
| GLP compliance: | Yes |
| QA statement: | Yes |
| Drug, lot #, and % purity: | 2151NM1 |

## Key Study Findings

Fluocinolone acetonide did not show any evidence of genotoxic activity in this *in vivo* test for induction of chromosome damage when tested in accordance with regulatory guidelines.

Methods

| | |
|---|---|
| Doses in definitive study: | FA: 0, 50, 100, 200 mg/kg; Mitomycin C: 6 mg/kg |
| Frequency of dosing: | Single intraperitoneal injection (IP) |
| Route of administration: | IP injection |
| Dose volume: | 20 mL/kg |
| Formulation/Vehicle: | 1% (w/w) Methylcellulose/ 0.5% (v/v) Polysorbate (tween) 80 in 0.9% Sodium Chloride for Injection, USP |
| Species/Strain: | CD®-1 (Swiss Crl:CD®-1(ICR)BR) albino outbred mice (*Mus musculus*) |
| Number/Sex/Group: | 5/sex/group for vehicle and test groups, 3/sex/group for positive control |
| Satellite groups: | None |
| Basis of dose selection: | In an integral dose range finding test (DRF), doses of 75, 150, and 200 mg/kg of FA were administered to groups of 3 mice/sex. Animals were observed for up to 2 days for signs of toxicity and/or mortality. Following evaluation of the results, there were no notable test article-related clinical signs. The maximum administrable dose was determined to be 200 mg/kg and this dose was therefore used as the high dose in the main test. |
| Negative control: | Vehicle, 1% (w/w) Methylcellulose/ 0.5% (v/v) Polysorbate (tween) 80 in 0.9% Sodium Chloride for Injection, USP |
| Positive control: | Mitomycin C |

**Text Table 1 Summary Design**

| Group | Material | Dosage (mg/kg) | Sampling time (hours) | Number of animals | |
|---|---|---|---|---|---|
| | | | | Male | Female |
| 1 | Vehicle | - | 24 | 5 | 5 |
| | | | 48 | 5 | 5 |
| 2 | FA | 50 | 24 | 5 | 5 |
| 3 | FA | 100 | 24 | 5 | 5 |
| 4 | FA | 200 | 24 | 5 | 5 |
| | | | 48 | 5 | 5 |
| 5 | Mitomycin C | 6 | 24 | 3 | 3 |

The sampling times were 24 and 48 hours. Animals were euthanised 24 or 48 hours after treatment, as indicated in the study design, and bone marrow smears were prepared. The bone marrow smears were fixed, temporarily stained with acridine orange, and examined under code using fluorescence microscopy. A total of 2000 immature erythrocytes (IE) per animal were examined for the presence of micronuclei indicative of chromosome damage. In addition, the proportion of immature erythrocytes in the total population (immature and mature erythrocytes, (ME)) was assessed for each animal as a measure of potential bone marrow toxicity.

## Study Validity

The data for the concurrent vehicle control (group mean % IE/(IE + ME) and micronucleated immature erythrocytes (MIE)) were close to the ranges determined from laboratory historical data. The positive control induced clear, unequivocal increases in micronuclei. Therefore, the performance of the vehicle and positive control was consistent with a valid assay.

## Results

No significant clinical sign of reaction to treatment or mortalities were observed for any of the treatment groups.
Animals treated with FA did not show any statistically significant increases in the number of micronucleated immature erythrocytes at either sampling time ($p > 0.01$). Individual and group mean values for animals treated with the vehicle or test article all fell close to or within the historical range for control animals. Mitomycin C caused large, highly significant increases ($p < 0.001$) in the frequency of micronucleated immature erythrocytes (MIE).
Animals treated with FA did not show any substantial increases in the incidence of micronucleated mature erythrocytes (MME) at either sampling time. The incidence of

micronucleated mature erythrocytes for all groups was uniformly low, confirming the absence of micronucleus-like artifacts.
It is concluded that Fluocinolone acetonide did not show any evidence of genotoxic activity in this *in vivo* test for induction of chromosome damage when tested in accordance with regulatory guidelines.

### 7.4 Other Genetic Toxicity Studies

None

# 8 Carcinogenicity

No carcinogenicity studies were conducted for Iluvien. The systemic exposure of FA from the 24-month rabbit ocular toxicity/pharmacokinetic study was below the limit of quantitation of 100-200 pg/mL. In the clinical study with Iluvien, the concentration of FA in the plasma was below the limit of quantitation of 100 pg/mL. Therefore, as stated in the Q&A at Pre-NDA Meeting of March 4, 2010, the waiver of carcinogenicity should be granted.

# 9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicity studies with Iluvien were not conducted. No reproductive and developmental toxicity studies were conducted for the marketed Retisert (NDA 21-737) either. Two published articles with FA were used as **the basis for Pregnancy labeling for Retisert.**
**1. Teratogenicity study of the new glucocorticosteroid budesonide in rabbits, I. Kihlstrom and C. Lundberg, Arzneim.-Forsch./Drug Res. 37: 43-6, 1987**
Fluocinolone acetonide when administered subcutaneously at dose of 0.13 mg/kg/day (approximately 10,000* times the daily clinical dose of Retisert), during Days 6 to 18 of pregnancy in the rabbit, induced abortion at the end of the third and at the beginning of the fourth gestational week.
**2. Toxicological Studies on Halopredone Acetate, L. Casilli et al, Arzneim-Forsch./Drug Res. 27: 2102-8, 1977**
FA when administered subcutaneously to rats and rabbits during gestation at a maternal toxic dose of 50 µg/kg/day (approximately 4,000* times the clinical dose of Retisert), fluocinolone
acetonide caused abortion and malformations in a few surviving fetuses.

The following is the **labeling for Retisert**:

No adequate animal reproduction studies have been conducted with fluocinolone acetonide.
Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels.
Fluocinolone acetonide when administered subcutaneously at dose of 0.13 mg/kg/day (approximately 10,000* times the daily clinical dose of Retisert), during Days 6 to 18 of

pregnancy in the rabbit, induced abortion at the end of the third and at the beginning of the fourth gestational week. When administered subcutaneously to rats and rabbits during gestation at a maternal toxic dose of 50µg/kg/day (approximately 4,000* times the clinical dose of Retisert), fluocinolone acetonide caused abortion and malformations in a few surviving fetuses.
There were no adequate and well-controlled studies in pregnant women. Retisert should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Note for Retisert labeling:** A class labeling for corticosteroids is used. Additional information for FA was taken from the published literature (as shown above) and the dose used in the study was maternal toxic.
(b) (4)

**For Iluvien, the class labeling for glucocorticoids should also be adopted.**
(b) (4)

(b) (4)

(b) (4)
The recommended labeling for Iluvien is listed in the **Executive Summary** of this review.

# 10 Special Toxicology Studies

No other toxicity studies have been performed for Iluvien.

# 11 Integrated Summary and Safety Evaluation

Iluvien® is a sterile sustained release intravitreal insert that is designed to release submicrogram levels of fluocinolone acetonide (FA) into the ocular vitreous chamber. The sustained-release intravitreal inserts that were investigated contained 0.19 mg of FA as the active ingredient, releasing FA at a target initial rate of 0.5 (ASI-001A) or 0.2 (ASI-002B) µg/day. Inactive ingredients are polyimide tubing, silicone adhesive and polyvinyl alcohol (PVA) and water for injection. The 0.2 µg/day version has a (b) (4) The Sponsor is seeking approval for the low dose version of Iluvien.
Polyvinyl alcohols (PVA) are synthetic polymers used since the early 1930s in a wide range of industrial, commercial, medical and food applications including resins, lacquers, surgical threads and food contact applications. Orally administered PVA is

relatively harmless, with $LD_{50}$ in the range of 15-20 g/kg. PVA has been used at up to (b) (4)% in the ophthalmic suspension/drop and at (b) (4) mg in the intravitreal implant (FDA approved drug list). The content of PVA in a 0.19 mg Iluvien is (b) (4) mg. The sponsor also conducted several biocompatibility studies with polyimide tubing and extracts of stainless steel injection needles. The results were negative.

A prior version of the drug delivery system, which is larger and requires surgical implantation, was used in Retisert® (Bausch & Lomb, Inc.), a FA-containing implant. Retisert is currently marketed for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye and is designed to release FA at a nominal initial rate of 0.6 µg per day. Iluvien is administered by intravitreal injection using a new delivery device.

The nonclinical toxicology program included a 24-month ocular toxicity and pharmacokinetics study in rabbits and a 9-month ocular toxicity study in rabbits using test article that had undergone forced degradation in an accelerated stability chamber. Continuous exposures of ocular tissues for both toxicity studies were achieved via one or two injections of the insert into the eye.

There appeared to be no definable toxicity associated with the administration of 0.2 µg/day FA. The test article, FA, appeared to induce posterior cortical/capsular cataracts in pigmented rabbits at 0.5 and 1.0 µg/day, as indicated by the increased incidence of cataracts at these concentrations. The development of these cataracts may be associated with the extended t1/2 of FA in the lens. There was no quantifiable systemic exposure of fluocinolone acetonide following intravitreal injection of Iluvien® intravitreal inserts to male and female Dutch Belted rabbits at 0.2, 0.5 and 1.0 µg/day doses (targeted release rates). The limit of quantitation of FA in the rabbit plasma was 100-200 pg/mL. The ocular concentrations declined very gradually following the first dose and then increased with the second dose at month 12 for the mid and high dose levels. The elimination of FA from the ocular tissues was very slow with elimination half-lives generally exceeding 2000 hours, and was not apparently tissue or dose dependent. The exposure of FA was generally highest in the choroid and pigmented epithelium followed by the lens or retina, the iris/ciliary body, the vitreous humor or cornea. The ocular exposure of FA in the aqueous humor was minimal at all dose levels in rabbits.

FA/Medidur test articles were placed in the 40°C/75% RH chamber for 6 months to generate exaggerated levels of degradation products in order to support the toxicity study objective. The total impurity level was (b) (4)% (w/w%), while the highest single impurity, the known degradant product (b) (4), was (b) (4)% (w/w%). The test article FA/Medidur, after undergoing forced degradation, did not appear to induce ocular disease or systemic toxicity over a 9-month period after its placement in the vitreous of pigmented rabbits.

The panel of genotoxicity tests performed by the Sponsor included the bacterial mutation test, mammalian cell mutation test and a mouse micronucleus test.

Fluocinolone acetonide did not show any evidence of genotoxic activity in these tests when tested in accordance with regulatory guidelines.

No carcinogenicity studies were conducted for Iluvien. Reproductive and developmental toxicity studies with Iluvien were not conducted. No reproductive and developmental toxicity studies were conducted for the marketed Retisert (NDA 21-737) either. Two published articles with FA were used as **the basis for Pregnancy labeling for Retisert.** In the proposed labeling for Iluvien, a class labeling for glucocorticoid is adopted but there is no mention of these published articles.

It is recommended that a labeling similar to that of Retisert should be used. (b) (4)

**The approval of NDA 201-923 is recommended.**

**Additional comment for internal discussion:**
During a Pre-NDA Meeting on 3-4-10 and a Meeting on 9-2-08, the following message was conveyed to the sponsor:
It is not clear whether there are any differences in formulation of CTM (Clinical Trial Materials) made by two different suppliers/manufacturers. Since the previous non-clinical ocular studies were conducted with different inserts made earlier, the pivotal 24-month rabbit ocular study should be conducted with the insert targeted for development and marketing. Please document any differences in the composition of the tested vs. the proposed clinical formulations. A similar comment was made during the 9-2-08 Meeting.
In the current NDA submission, the sponsor stated the following:
The Iluvien insert for the intended market product contains 0.19 mg of FA. There is a slight difference in the total FA content between the product used in the preclinical and clinical studies and the product to be marketed, i.e., the FA content of the product manufactured at pSivida averaged (b) (4) mg. However, the formulation used (b) (4) remained the same (b) (4) for the preclinical/clinical studies and the product to be marketed. FA is released from the polyimide tube at sub-microgram levels (b) (4)
It appears that the Iluvien formulation targeted for marketing was not studied in the pivotal 24-month rabbit ocular study. No explanation was given by the sponsor. Although the difference between formulations may be small, it is not clear why the safety/toxicity of the drug product for marketing was not studied.
Through the personal communication with chemistry reviewer, it was found that the proposed impurity level for drug product specification by the sponsor is not more than the level contained in the batch used in the 9-month rabbit ocular study (Lot. No. 311-6, Following a Forced Degradation of the Test Article). Therefore, the contents of impurities in the formulations may not cause any additional toxicity problem.

If other disciplines (clinical, clinical pharmacology and chemistry reviewers) would be satisfied with the explanation given by the sponsor for the differences in formulations, the pharmacology reviewer would not insist on repeat of the 24-month rabbit ocular study.

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/s/

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CONRAD H CHEN
11/15/2010

WENDELYN J SCHMIDT
11/17/2010

I concur with the Dr. Chen's assessment of the acceptability and interpretation of the pharmacologic and toxicologic data in this NDA.

# PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

**NDA Number: 201-923** **Applicant: Alimera Sciences, Inc.** **Stamp Date: June 28, 2010**
**Drug Name: Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg**

**IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? Yes [ X ] No [ ]**

**The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.**

| | Parameters | Yes | No | Comment |
|---|---|---|---|---|
| 1 | On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin? | X | | |
| 2 | Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review begin? | X | | |
| 3 | On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin? | X | | |
| 4 | Are ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? | X | | |
| 5 | If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made a appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required? | X | | |
| 6 | Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in $mg/m^2$ or comparative serum/plasma levels) and in accordance with 201.57? | | X | The recalculated multiples will be recommended in the labeling. |
| 7 | Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions? | X | | |
| 8 | On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route? | X | | |
| 9 | Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? | X | | |
| 10 | Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? | X | | |
| 11 | From a pharmacology perspective, is this NDA fileable? | X | | |

**Note:**

Reviewing Pharmacologist: 10-6-2010

Conrad Chen, Ph.D. Date:

Team Leader:

Wendelyn Schmidt, Ph.D. Date

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

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/s/

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CONRAD H CHEN
10/06/2010

WENDELYN J SCHMIDT
10/07/2010