

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210331Orig1s000

OTHER REVIEW(S)



Biocompatibility review

NDA210331: (b) (4), 0.18 mg Intravitreal Implant

Date: July 6, 2018
To: The Record
From: Simona Bancos, Ph.D., Biologist, CDRH/DOED
Subject: NDA 210331
Drug product: (b) (4), 0.18 mg Intravitreal Implant
Sponsor: pSivida US

Purpose:

The sponsor submitted a New Drug Application (NDA) for (b) (4) a fluocinolone acetonide (FA)-containing drug product. (b) (4) is an injectable implant administered by intravitreal injection through *pars plana* and it is designed to continuously deliver fluocinolone acetonide (FA) in the vitreous for approximately 36 months.

In an email dated June 8, 2018, Dr. Yong Wang (CDER) requested that CDRH reviews the biocompatibility test reports provided for the polyimide tube and “address the biocompatibility and safety of the syringe system.”

Per CDER’s request, the current document contains the biocompatibility review of the polyimide tubing and the applicator.

Indications for use (excerpts from NDA 210331):

(b) (4) is intended for use for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

Product Description (excerpts from NDA 210331):

The drug product is comprised of the following components:

- FA, the active pharmaceutical ingredient,
- The polyimide tube, and
- The applicator.

FA is a member of a class of fluorinated synthetic corticosteroids. FA had been previously used in other FDA-approved ophthalmic drug products (Vitrasert, Retisert, Iluvien, etc.). (b) (4)

[Redacted text block]

The Applicator



The components of the container closure

Component	Part Number	Specifications	Drawing	Materials	Product Contact	Vendor/Supplier
(b) (4)						



Biocompatibility testing conducted on the polyimide tubing (excerpts from NDA 210331):

The sponsor states that the manufacturer of the polyimide tube performed acute systemic toxicity, intra-cutaneous toxicity and implantation testing on the tube and concluded that the polyimide tube meets USP Class VI Biocompatibility requirements.

The sponsor states that the same polyimide tube, silicone adhesive and PVA membrane had been used in the FDA-approved ILUVIEN drug product (NDA 201923, approved in 2014). (b) (4)

(b) (4) The sponsor provided the right to reference NDA 201923.

(b) (4)

Biocompatibility testing conducted on applicator

The sponsor did not provide biocompatibility information on the applicator.

Reviewer's comment:

As summarized on page 3 of this review, the applicator contains several components (b) (4)

The needle assembly has direct limited contact (< 24h) with the patient. For these type of devices, we recommend that cytotoxicity, sensitization and irritation be conducted on the components of the needle assembly that directly contact the patient. In addition, the needle assembly had direct contact with the (b) (4) Although the needle assembly is manufactured (b) (4), a material widely used for medical devices, the sponsor needs to provide in additional information to demonstrate that during storage there are no impurities that are transferred from the needle and/or (b) (4) ultimately to the patient's eye. In addition, the applicant needs to demonstrate that the components of the needle and applicator that have direct contact with the patient (b) (4) do not induce cytotoxicity, sensitization and irritation/intracutaneous reactivity.

Reviewer's conclusion:

In the current document, I provided biocompatibility review of the polyimide tubing and applicator. I concluded that the biocompatibility profile of the polyimide tubing is acceptable. However, I recommend that the following is conveyed to the sponsor regarding the lack of biocompatibility data for the applicator:

You state (Section 3.2.P.1, Description and Composition of the Drug Product)

(b) (4)



(b) (4). Therefore, to adequately evaluate the safety use of the applicator, please provide biocompatibility testing on the applicator. The testing should include cytotoxicity, sensitization, irritation/intracutaneous reactivity on the 25-gauge needle. In addition, please provide cytotoxicity, sensitization, irritation/intracutaneous reactivity, and systemic toxicity/physico-chemical testing on the components of the applicator that have direct contact with the drug core.

For additional details regarding the recommended biocompatibility testing please refer to “Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. “

Memorandum

Date: July 5, 2018
From: Don Calogero _____
Biomedical Engineer, CDRH/ODE/DOED
To: The Record
Subject: Biomedical Engineering Review – NDA CMC PAS 210331
Device: (b) (4) (fluocinolone acetonide) implant 0.18mg
Sponsor: pSvida

Introduction

pSvida has submitted this NDA for the (b) (4) (fluocinolone acetonide) implant 0.18mg. This is a sterile sustained release drug delivery system that is designed to release sub-microgram levels of fluocinolone acetonide (FA) into the ocular vitreous chamber.

This review does not address any of the drug components of this implant and only evaluates device related issues. The specific request was to review the transport stability study performed by the manufacturer.

Device Description



Figure 2: Applicator

(b) (4)



Transport Stability Study

The manufacturer has contracted with (b) (4) to perform the package evaluation testing. This testing was to evaluate the capabilities of the package design for the (b) (4) implant when exposed to conditions representative of the production and shipping and handling stresses likely to occur during the products life. Testing was done under controlled laboratory conditions with equipment qualified to perform these tests.

The packaging that was evaluated is described below.

Primary Package

The primary package consisted of a dual barrier pouch. The inner is foil pouch and the outer is a Tyvek (b) (4) pouch.

Secondary Package

The secondary package was a (b) (4) box (b) (4).

Shipping Unit

(b) (4)

The following equipment was used for this testing.

Equipment Name	Model No.	Serial No.	Calibration Due
L.A.B. Accudrop 160 Drop Tester	160	1064042	Height verified with tape measure
MTS Vibration Test System	891	800.50-55B	11-Aug-06
Small Compression Test System	842.36	800.50-55C	25-Aug-06
T.M. Electronics Package Tester	BT-100	BT-456	24-Jul-06
Gaynes Rotary Vibration Shaker Table	none	4958	25-Apr-06
Tenney Altitude Chamber (23)	27ST	10844	Dependant upon vacuum gauge
Thermal Couple Probe	TTSS-HH	D20	01-May-06

This test was based on ASTM D 4169-05, DC 13, Assurance Level I Truck/Air Spectrum. The packaged product, as described previously, was subjected to the following four schedules.

Schedule A – manual handling

This testing is designed to determine the ability of the shipping unit to withstand the hazards occurring during manual handling such as loading, unloading, stacking, sorting, or palletizing. The main hazards from these operations were the impacts caused by dropping or throwing. The test methods are described in ASTM D4169 Manual Handling First Drop Sequence.

Schedule C – vehicle stacking

This testing is designed to determine the ability of the shipping unit to withstand the compressive loads that occur during vehicle transport. The required loading must consider, in addition to the overload, the effects of length of time in storage, vibration, the alignment or stacking pattern of the container, variability in container strength, moisture content, temperature, previous handling, and method of load support.

Schedule F – loose load vibration

This testing is designed to determine the ability of the shipping unit to withstand the repetitive shocks occurring during transportation of bulk or loose loads.

Schedule E – vehicle vibration

This testing is designed to determine the ability of the shipping unit to withstand the vertical vibration environment during transportation.

[It should be noted that schedule F was performed before schedule E in the testing sequence.]

After these schedules were performed, the packaging integrity was assessed using the bubble leak test as described in ASTM F 2096-04. The inner and outer pouches were assessed with the bubble leak test after the schedules described above were performed on the test samples. Thirty inner pouches and thirty outer pouches were tested. No failures were reported.

Recommendation

The manufacturer has adequately validated that the proposed packaging configuration and shipping methods are compatible and do not compromise the packaging integrity. No additional information is needed.

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/s/

ASHLEY N WALLACE
10/15/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 5, 2018

To: June Germain
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 210331**
YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg, for
intravitreal injection

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on September 26, 2018, for YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection. OPDP's comments are provided directly below on the attached marked-up copy of the proposed PI. Our comments are based on the version of the proposed PI sent via email from DTOP (June Germain) on October 2, 2018.

Thank you for your consult. If you have any questions on our comments for the proposed labeling, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CARRIE A NEWCOMER
10/05/2018

Clinical Inspection Summary

Date	August 20, 2018
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	William Boyd, M.D., Clinical Team Leader Martin Nevitt, M.D., Clinical Reviewer June Germain, Regulatory Project Manager
NDA#	210331
Applicant	EyePoint Pharmaceuticals, Inc.
Drug	Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg
NME	No
Review Priority	Standard
Proposed Indication	Treatment of non-infectious uveitis affecting the posterior segment of the eye
Consultation Request Date	February 5, 2018
Summary Goal Date	September 12, 2018
Action Goal Date	October 12, 2018
PDUFA Date	November 5, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical site of Dr. Foster was inspected in support of this NDA. Due to the fact that the protocol-specified blinding process was not followed at Dr. Foster's site, we recommend that DTOP conduct a sensitivity analysis excluding the data from this investigator site. Otherwise, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication. The final compliance classification of this inspection was Voluntary Action Indicated (VAI).

II. BACKGROUND

The Applicant submitted this NDA to support the use of Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg for the treatment of non-infectious uveitis affecting the posterior segment of the eye

An inspection was requested for the following protocol in support of this application:

Protocol PSV-FAI-001, "A Phase III, Multi-national, Multi-center, Randomized, Masked, Controlled, Safety and Efficacy Study of a Fluocinolone Acetonide Intravitreal (FAI) Insert in Subjects with Chronic Non-Infectious Uveitis Affecting the Posterior Segment of The Eye"

This study was conducted at 39 study sites in six countries enrolling 129 subjects.

The primary objectives of this study were to evaluate the safety and efficacy of a FAI insert in the management of subjects with chronic non-infectious uveitis affecting the posterior segment of the eye.

The primary efficacy endpoint for this study was the proportion of subjects who had a recurrence of uveitis in the study eye within 6 months after receiving study treatment where recurrence was defined as:

- A > 2 step increase in the number of cells in the anterior chamber per high powered field (1.6 X using a 1-mm beam), compared to any visit time point prior to Month 6
- OR
- An increase in the vitreous haze of > 2 steps, compared to any visit time point prior to Month 6
- OR
- A deterioration in visual acuity of at least 15 letters BCVA, compared to any visit time point prior to Month 6

Rationale for Site Selection

The clinical site of Dr. Foster was selected for inspection because of its relatively large enrollment and lack of previous inspections.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site #18 C. Stephen Foster, M.D. Ocular Immunology and Uveitis Foundation 1440 Main Street, Suite 201 Waltham, MA 02451 Ph: (781) 891-6377 Previously: Ocular Immunology and Uveitis Foundation 5 Cambridge Center, 8 th Floor Cambridge, MA 02142	PSV-FAI-001 Subjects: 13	9-21 May 18	VAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

1. C. Stephen Foster, M.D.

At this site for Protocol PSV-FAI-001, 14 subjects were screened, and 13 subjects were randomized to treatment. The records of all 13 randomized subjects were reviewed. Informed consent was obtained appropriately from all subjects enrolled in the study prior to any study-related activities.

Other records reviewed included Institutional Review Board correspondence and approvals, monitoring correspondence, financial disclosure forms, sponsor and monitor correspondence, study protocol and amendments, inclusion/exclusion criteria, randomization schemes, adverse events, primary efficacy outcomes, source documentation, electronic subject data, and drug accountability records.

A Form FDA 483 was issued at the conclusion of the inspection. The 483 noted that the protocol-specified blinding process was not followed. In brief, the protocol stated that one investigator would be unblinded to the treatment arm and would perform the study procedure on Day 1 while a blinded investigator would perform all safety and efficacy assessments after Day 1. The unblinded investigator (Dr. Foster) not only did the procedures on Day 1 but also conducted follow up safety and efficacy assessments on at least 32 occasions for seven of thirteen enrolled subjects:

Subject	Visit	Visit Date
(b) (6)	Day 28	(b) (6)
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Day 7	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	

(b) (6)	Unscheduled	(b) (6)
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	
	Unscheduled	

This potential source of bias was discussed with Dr. Boyd, the medical team lead for DTOP. He said that it was unlikely that the unblinding would have had a significant effect on study results; however, DTOP would perform sensitivity analyses excluding this investigator site to evaluate the effect on the efficacy and safety results and would include a full discussion within their Clinical Review.

The Form FDA 483 also noted that Subject (b) (6) was injected with the test article under Protocol PSV-FAI-001 on (b) (6). he subject was seen for unscheduled visits on (b) (6), this same subject was randomized and dispensed the test article for another study (b) (4)

This subject was enrolled in the comparator arm of the study and received prednisolone acetate ophthalmic suspension (Pred Forte). Dr. Foster agreed that the subject, being in follow up status for one study, should not have been enrolled in the other.

Dr. Foster responded in writing in an undated letter to the observations on the Form FDA 483. With respect to potential unblinding, Dr. Foster noted that if the masked investigator was unavailable, he would conduct safety and efficacy assessments at scheduled and unscheduled visits. He stated that he did not discuss treatment assignment with the masked investigator or other masked study personnel. Dr. Foster acknowledged that his misinterpretation of protocol requirements led to the enrollment of Subject (b) (6) in concurrent studies. Dr. Foster's written response and proposed corrective measures appear adequate.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.\NDA 210331
DTOP\Division Director\ Renata Albrecht
DTOP\Team Leader\William Boyd
DTOP\Medical Officer\Martin Nevitt
DTOP\Project Manager\June Germain
OS\DCCE\Division Director\Ni Khin
OS\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OS\DCCE\GCPAB\Team Leader\Phillip Kronstein
OS\DCCE\GCPAB\Reviewer\Roy Blay
OS\DCCE\Program Analysts\Yolanda Patague
OS\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
08/20/2018

PHILLIP D KRONSTEIN
08/20/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 2, 2018
Requesting Office or Division:	Division of Transplant and Ophthalmology (DTOP)
Application Type and Number:	NDA 210331
Product Name and Strength:	Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	EyePoint Pharmaceuticals US, Inc.
FDA Received Date:	May 4, 2018
OSE RCM #:	2018-71
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW VS REASON FOR REVIEW

As part of the approval process for Yutiq (fluocinolone acetonide) intravitreal implant 0.18mg the Division of Transplant and Ophthalmology (DTOP) requested that we review the proposed packaging, label and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C - N/A
FDA Adverse Event Reporting System (FAERS)*	D - N/A
Other	E - N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 include the identified medication error issues with the submitted carton labeling and container labels, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Transplant and Ophthalmology Products (DTOP)

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			
1.	Step 13, within subsection 2.2 of the PI, instructs the user to 'discard' the applicator after use but does not	Inconsistent instruction on proper disposal of the applicator could lead to patient or healthcare provider harm.	To avoid improper disposal and for consistency across labeling, add specific disposal instructions to the

	detail specifically how to dispose of the applicator. In contrast, the side view of the carton labeling contains a statement instructing the user to “Dispose of the applicator safely in biohazard sharps container”.		administration steps within subsection 2.2. For example: “Step 13. Remove the YUTIQ applicator from the eye and dispose of the applicator safely in a biohazard sharps container.”
Full Prescribing Information			
1.	The dosage of the implant is not included in section 2.1 of the Dosage and Administration section.	All necessary dosage information must be included in order to avoid medication errors.	In section 2.1, add the product dosage, “0.18 mg”.

Table 3: Identified Issues and Recommendations for EyePoint Pharmaceuticals (entire table to be conveyed to Applicant)

Container Labels- Outer Pouch Labeling and Inner Pouch Labeling			
1.	Container label on inner pouch is missing lot number, expiration date and name of manufacturer/packer/ drug distributor.	To avoid dispensing errors, lot number and expiration date must be included on the container label. ^a	Designate an area for inclusion of the lot number, expiration date and name of manufacturer, packer, or distributor on the inner pouch container label. We also recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.
Carton Labeling			
1.	(b) (4)	To avoid medication errors and product selection errors, the proprietary name, established name, and product strength should be the most	Consider removing or relocating (b) (4)

	(b) (4)	prominent information presented on the carton labeling. ^a (b) (4)	
2.	The carton content information presented on the end view of the carton labeling is duplicated on the Principal Display Panel (PDP).	To avoid redundancy, carton content information must be available to the user in a format that is easy to read and easily accessible.	In order to display carton contents on the PDP more clearly, consider changing the content statement to the following: “This carton contains: One sterile- single use only intravitreal implant in applicator with 25 gauge needle. Each implant contains 0.18 mg of fluocinolone acetonide in polyimide drug delivery system. Excipients: Polyvinyl Alcohol; Silicone Adhesive. One package insert.” All other information, not related to carton contents, can be displayed separately from carton content information.

4 CONCLUSION

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Yutiq that EyePoint Pharmaceuticals submitted on January 5, 2018.

Table 4. Relevant Product Information for Yutiq	
Initial Approval Date	N/A
Active Ingredient	fluocinolone acetonide
Indication	treatment of chronic non-infectious uveitis affecting the posterior segment of the eye
Route of Administration	intravitreal injection
Dosage Form	Implant
Strength	0.18 mg
Dose and Frequency	One implant in the affected eye. (b) (4)
How Supplied	The applicator (pre-loaded with the implant) is placed within two sealed pouches, which are placed in a carton.
Storage	Store (b) (4) 25°C. (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 6, 2018, we searched the L:drive and AIMS using the terms, Yutiq, ^{(b) (4)} and fluocinolone to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified did not identify any results.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Yutiq labels and labeling submitted by EyePoint Pharmaceuticals on May 4, 2018.

- Container labels (outer and inner pouch)
- Carton labeling
- Prescribing Information (Image not shown)

F.2 Label and Labeling Images

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling:



Container Label- Outer Pouch Label:



Container Label- Inner Pouch Label:

(b) (4)



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NASIM N ROOSTA
07/02/2018

OTTO L TOWNSEND
07/02/2018