

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210331Orig1s000

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/BLA REVIEW AND EVALUATION

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07/06/2018, 08/08/2018
Product: Fluocinolone Acetonide Intravitreal implant in
applicator, 0.18 mg
Indication: Treatment of non-infectious uveitis affecting the
posterior segment of the eye
Applicant: EyePoint Pharmaceuticals, Inc
(Previously, pSivida Corp)
Review Division: DTOP
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1 Executive Summary

1.1 Introduction

The Applicant, EyePoint Pharmaceuticals, Inc (previously named pSivida Corp) submitted NDA 210331 under the 505(b)(1) pathway for YUTIQ™ (Fluocinolone Acetonide Intravitreal implant in applicator, 0.18 mg), to treat non-infectious uveitis affecting the posterior segment of the eye, which included proposed labeling text to comply with the “Pregnancy and Lactation Labeling Rule” (PLLR).

1.2 Brief Discussion of Nonclinical Findings

- Applicant has the right of reference to NDA 201923 for Iluvien® (fluocinolone acetonide) intravitreal implant 0.19 mg.
- QSAR assessment of mutagenic potential was conducted for degradation products (b) (4)

In Applicant’s responses to Agency information request (IR), dated 8/8/18 and 08/13/2018, the Applicant stated that a referenced mutagenicity study provides support that impurities were not mutagenic under study conditions.

- The proposed specification levels (b) (4) per ICHQ3B. In the aforementioned IR responses, the Applicant proposed to revise the limits to NMT (b) (4) % in the drug product specification.
- Changes in Sections 8.1, 8.2 and 13 Applicant-proposed labeling text were made to comply with “Pregnancy and Lactation Labeling Final Rule”.

1.3 Recommendations

1.3.1 Approvability

No issues were identified that would affect approvability, presuming Applicant adjusts limits (b) (4) to levels that are consistent with ICH Q3B guideline recommendations.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

This reviewer recommends the following editorial changes in Sections 8.1, 8.2, 8.4 and 13 according to “Pregnancy and Lactation Labeling Final Rule”.

Applicant's Proposed Text	Reviewer's recommendations
<p>8.1 Pregnancy</p> <p>Risk Summary</p> <div style="background-color: #cccccc; height: 300px; width: 100%;"></div>	<p>8.1 Pregnancy</p> <p><u>Risk Summary</u></p> <p>Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug-associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.</p> <p>All pregnancies have a risk of birth defect, loss, or other adverse outcomes.</p>
<p>In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.</p>	<p>In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.</p> <p><i>[We defer assessment of the adequacy of clinical data and associated proposed labeling language to the clinical team]</i></p>
<p>8.2 Lactation</p> <p>Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects.</p> <div style="background-color: #cccccc; height: 100px; width: 100%;"></div>	<p>8.2 Lactation</p> <p><u>Risk Summary</u></p> <p>Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Clinical or nonclinical lactation studies have not been conducted with YUTIQ.</p>

<p>It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production.</p> <p style="text-align: right;">(b) (4)</p>	<p>It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production.</p>
<p>The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ.</p>	<p>The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed infant from YUTIQ.</p>
<p>13 NONCLINICAL TOXICOLOGY</p> <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>Long-term animal studies have not been conducted to determine the carcinogenic potential or the effect on fertility of YUTIQ.</p> <p>Fluocinolone acetonide was not genotoxic <i>in vitro</i> in the Ames test (S. typhimurium and E. coli) and the mouse lymphoma TK assay, or <i>in vivo</i> in the mouse bone marrow micronucleus assay.</p>	<p>13 NONCLINICAL TOXICOLOGY</p> <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>Long-term animal studies have not been conducted to determine the carcinogenic potential or the effect on fertility of YUTIQ.</p> <p>Fluocinolone acetonide was not genotoxic <i>in vitro</i> in the Ames test (S. typhimurium and E. coli) and the mouse lymphoma TK assay, or <i>in vivo</i> in the mouse bone marrow micronucleus assay.</p>

2 Drug Information

2.1 Drug

Generic Name

Fluocinolone Acetonide Intravitreal implant; Fluocinolone Acetonide Intravitreal insert

Code Name

FAI insert

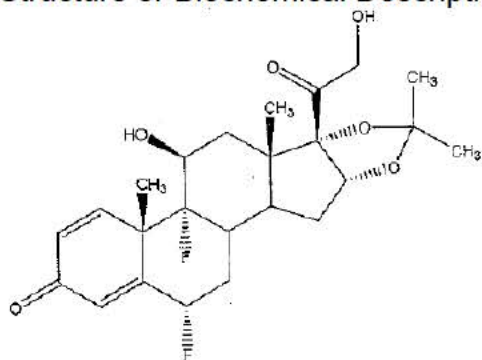
Chemical Name

pregna-1,4-diene-3,20-dione,6,69-difluoro-11,21,dihydroxy-16,17-[(1-methyl-ethylidene)bis(oxy)]-,6 α ,11 β ,16 α)

Molecular Formula/Molecular Weight

C₂₄H₃₀F₂O₆; MW: 452.50 g/mol

Structure or Biochemical Description



Pharmacologic Class

Synthetic fluorinated corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

Per submission (EDR: Module 1.4.2), the Applicant has submitted "right of reference" to NDA 201923 for Iluvien® (flucinolone acetonide) intravitreal implant 0.19 mg.

The Applicant has right of reference to Drug Master File (DMF) (b) (4) for flucinolone acetonide CMC processes and formulation data.

2.3 Drug Formulation

Per Nonclinical review by Dr. Aaron Ruhland dated 5/10/2012 under IND #113140: ¹

The composition of the FAI insert is the same as the composition of the Iluvien insert with respect to active ingredient (FA), (b) (4) (b) (4) (b) (4)

(b) (4) *The formulation of Iluvien contains 0.19 mg of FA.* (b) (4)

Per label of Iluvien® (flucinolone acetonide) intravitreal implant:²

¹ DARRTS: IND #113140, REV-NONCLINICAL-03(General Review), by RUHLAND, AARON M, dated 5/10/2012

² https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/201923s000lbl.pdf

ACTIVE INGREDIENT/ACTIVE MOIETY		
Ingredient Name	Basis of Strength	Strength
FLUOCINOLONE ACETONIDE (UNII: 0CD5FD6S2M) (FLUOCINOLONE ACETONIDE - UNII:0CD5FD6S2M)	FLUOCINOLONE ACETONIDE	0.19 mg

INACTIVE INGREDIENTS	
Ingredient Name	Strength
POLYVINYL ALCOHOL (UNII: 532B59J990)	
WATER (UNII: 059QF0K00R)	

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

On 7/5/2018, CMC requested P/T investigate “if the following known impurities are properly qualified at the following levels:”

Degradation Products	
(b) (4)	NMT (b) (4) %
	NMT %
	NMT %
	NMT %
	NMT %
	NMT %
Total degradation products	NMT

(excerpted from internal email communication)

In addition, CMC informed P/T that (b) (4) in an earlier internal email communication (dated 5/31/2018), which prompted submission of a consult to the CDER Computational Toxicology Consulting Service for a QSAR assessment of mutagenic potential (b) (4)

Since the Applicant cross-referenced NDA 201923 (LOA submitted), to verify whether the proposed degradation products were qualified, this reviewer accessed the Study Report of “9-month Ocular Toxicity Study of Intravitreal Administrated FA/Medidur™ (Fluocinolone Acetonide Sustained Release Insert) to Pigmented Rabbits Following a

Forced Degradation of the Test Article” (Study # JOK00001) under NDA 201923. The test article FA/Medidur, after undergoing forced degradation, did not appear to induce ocular toxicity or systemic toxicity over a 9-month period after its placement in the vitreous of pigmented rabbits.

Per APPENDIX 2 - STABILITY OF DOSE FORMULATIONS (pg143 of 606) in the study report:

Table 1. Certificate of Analysis for the Batch used in 9-month Rabbit Study in NDA 201923



As shown in the **Table 1** above, in the study using Iluvien following forced degradation, (b) (4) levels were detected up to (b) (4)% (w/w) in a single insert. The 9-month nonclinical study in pigmented rabbits used two inserts in a single eye, thus (b) (4) levels was qualified at (b) (4)% in the combined inserts designed to release drug substance at a rate of (b) (4) µg/day ((b) (4)). Hence, the proposed (b) (4) levels of NMT (b) (4)% is adequately qualified.

This reviewer generated the following table to compare the Applicant-proposed degradation product specification levels with the levels in the 9-month nonclinical rabbit study or ICHQ3B:

Table 2. Degradation Product Specification Levels

Degradation Product	Level in the forced-degraded Illuvien (w/w%)	Level per eye in 9-month ocular toxicity pigmented rabbit study (w/w%)	Currently proposed level for YUTIQ (w/w%)	Qualified by nonclinical data or less than ICH Q3B qualification threshold? (If no, P/T recommendations provided below the table)
(b) (4)				Yes
				Yes
				No ¹
				No ²
				Acceptable, per ICHQ3B.
				Acceptable, per ICHQ3B.

Reviewer Notes:

- ¹ For (b) (4):
- Applicant stated that these two impurities could not be separated via HPLC, and provided an acceptance criteria ((b) (4) %) for degradation product (b) (4) that exceeded ICHQ3B qualification limits.
 - CDER Computational Toxicology Consulting Service conducted QSAR assessment of mutagenic potential for degradation product (b) (4) was predicted to be positive for bacterial mutagenicity.

- As such, Applicant should follow ICH M7 guidance, and provide necessary data/information to support safety.
 - If found to be non-mutagenic, then Applicant should ensure that acceptance criteria for degradation product (b) (4) does not exceed the ICH Q3B qualification limit. Alternatively, Applicant can provide safety data to qualify degradation product (b) (4) at a level that exceeds the ICH Q3B qualification threshold.
 - If found to be mutagenic, the degradation product (b) (4) impurity(ies) should be adequately controlled. It should be noted that a TTC exists for systemic safety (see ICH M7), but a TTC does not exist for ocular safety. The Applicant will need to provide justification for both systemic and ocular safety, along with supporting safety data.

² For (b) (4):

- Actual and potential degradation products likely to be present in the final drug product should be assessed for mutagenic potential, per ICH M7.
- Justification for acceptance criteria that exceed qualification limits, per ICHQ3B, should include safety (qualification) data to support proposed level.
- Please provide these data, and/or an adequate control strategy to ensure safety.

On 7/25/2018, CMC sent the Applicant an information request (IR) regarding the above impurities (b) (4)

In Applicant-submitted responses to IR (SD16 and SD18) dated 8/8/2018 and 8/13/2018, respectively:

Degradation product (b) (4)

- Applicant stated that it “will conduct a bacterial mutagenesis study of degradation product (b) (4) and will submit the results of that study to FDA as soon as the study report is available. The bacterial mutagenesis study will use (b) (4) as the test article; (b) (4) is degradation product (b) (4) and is commercially available in sufficient amounts”, and “has revised the proposed commercial drug product specification for degradation product (b) (4) impurity(ies), from NMT (b) (4) % to NMT (b) (4) %”.
- Applicant has also justified that bacterial mutagenesis study has been conducted under the cross-referenced NDA #201923:

In this study, the test article was fluocinolone acetonide (b) (4) batch number 2151NM1. The certificate of analysis for this batch is presented in Appendix 1 of the study report and lists (b) (4) as present at (b) (4) % (w/w) in the batch. The maximum amount of fluocinolone acetonide that was applied per plate in this study was 5000 µg/plate (Text Table 1 of study 961864 report) in a total volume of 2.7 mL; the corresponding maximum amount of (b) (4) that was applied per plate in this study was (b) (4) per plate, in a total volume of 2.7 mL, yielding a concentration of (b) (4) g/mL.

- Ames test result was assessed negative under conditions of this study, per the P/T review by Dr. Conrad H. Chen under NDA #201923. This reviewer accessed the AMES study report (# 961864):

Table 3. Certificate of Analysis for Batch used in AMES Test in NDA 201923

(b) (4)

- As shown in the Table 3 above, (b) (4) was listed as present at (b) (4) % (w/w) in the batch. This reviewer agrees with the firm's calculation that the maximum amount of (b) (4) applied per plate in this study was (b) (4) per plate, in a total volume of 2.7 mL, yielding a concentration of (b) (4) µg/mL.
- At the proposed specification limit of (b) (4) %, the maximum amount of degradation product (b) (4) will be: (b) (4) (b) (4) which is less than the tested (b) (4) per plate.
- Regarding ocular genotoxicity, Applicant justified that:
The data in study 961864 show that degradation product (b) (4) impurity(ies) does not have bacterial mutagenic activity at a concentration as high as (b) (4) µg/mL. This concentration of the impurity in the experiment exceeds the predicted corresponding concentration of this impurity in the human vitreous ((b) (4) µg/mL), if the entire contents of a YUTIQ

implant were available immediately. This calculation is based on the following assumptions:

- Minimum adult human vitreous volume: $(b)_{(4)} \text{cm}^3$
- Maximum amount of degradation product $(b)_{(4)}$ (ies) (using EyePoint's revised proposed specification of NMT $(b)_{(4)}\%$; $(b)_{(4)}$: approximately $(b)_{(4)} \mu\text{g}$

The data from study 961864 support the proposed impurity limit of NMT $(b)_{(4)}\%$ for degradation product $(b)_{(4)}$ impurity(ies) in YUTIQ implants.

- As such, this reviewer considers it acceptable for Applicant to adjust the limit of degradation product $(b)_{(4)}$ to NMT $(b)_{(4)}$ in the drug product specification.

$(b)_{(4)}$

- Applicant stated it "has initiated a QSAR assessment" for mutagenic potential. If the assessment indicates mutagenic potential, it "will conduct a bacterial mutagenesis study of $(b)_{(4)}$ and will submit the results of that study to FDA". In addition, Applicant "has revised the proposed commercial drug product specification for $(b)_{(4)}$ from NMT $(b)_{(4)}\%$ to NMT $(b)_{(4)}\%$ ".
- Applicant justified that bacterial mutagenesis study has been conducted under the cross-referenced NDA #201923:

In this study, the test article was fluocinolone acetonide $(b)_{(4)}$ batch number 2151NM1. The certificate of analysis for this batch is presented in Appendix 1 of the study report and lists $(b)_{(4)}$ as present at $(b)_{(4)}\%$ (w/w) in the batch. The maximum amount of fluocinolone acetonide that was applied per plate in this study was 5000 $\mu\text{g}/\text{plate}$ (Text Table 1 of study 961864 report) in a total volume of 2.7 mL; the corresponding maximum amount of $(b)_{(4)}$ that was applied per plate in this study was $(b)_{(4)}$ per plate, in a total volume of 2.7 mL, yielding a concentration of $(b)_{(4)}$ EyePoint has revised the proposed commercial drug product specification for $(b)_{(4)}$, from NMT $(b)_{(4)}\%$ to NMT $(b)_{(4)}\%$. This revised specification will reduce the calculated maximum permitted level of this impurity in an individual YUTIQ implant to $(b)_{(4)} \mu\text{g}$ $(b)_{(4)}$

- Ames test result was assessed negative per the P/T review by Dr. Conrad H. Chen under NDA #201923. This reviewer accessed the AMES study report (# 961864) and agrees with the firm's conclusion.
- Regarding ocular genotoxicity, Applicant justified that:
The data in study 961864 show that $(b)_{(4)}$ does not have bacterial mutagenic activity at a concentration as high as $(b)_{(4)} \mu\text{g}/\text{mL}$. This concentration exceeds the predicted corresponding concentration of this

impurity in the human vitreous (b) (4) $\mu\text{g/mL}$), if the entire contents of a YUTIQ implant were available immediately. This calculation is based on the following assumptions:

- Minimum adult human vitreous volume (b) (4); (b) (4) cm^3
- Maximum amount of (b) (4) (using EyePoint's revised proposed specification of NMT (b) (4) %; (b) (4) approximately (b) (4) μg

The data from study 961864 support the proposed impurity limit of NMT (b) (4) % for degradation product (b) (4) impurity(ies) in YUTIQ implants.

- As such, this reviewer considers it acceptable for Applicant to adjust the limit of (b) (4) to NMT (b) (4) %.

On 8/24/2018, Applicant submitted a QSAR analysis report through email communication, and predicted all impurities, (b) (4) to be negative for bacterial mutagenicity. These impurities were further evaluated by CDER Computational Toxicology Consultation Service for bacterial mutagenicity using (Q)SAR models. (note, the Applicant historically uses two different chemical structures interchangeably to refer to (b) (4) where only one was analyzed in its report. CDER Computational Toxicology evaluated both structures for (b) (4)

The consult concluded:

Overall, the Agency agrees with the Sponsor's conclusions that two of the impurities lack mutagenic potential. However, (b) (4) is predicted by the Agency to be positive for bacterial mutagenicity.

However, Applicant has referenced the bacterial mutagenesis study (report # 961864) under NDA #201923. As discussed above, for Degradation product (b) (4) (pages 11 -12 of this review), the referenced study provides support that impurities were not mutagenic under the conditions of the conducted study. In addition, applicant proposed to revise the limits to NMT (b) (4) %.

2.6 Proposed Clinical Population and Dosing Regimen

Per the proposed labeling:

- YUTIQ, a non-bioerodible intravitreal implant in a drug delivery system containing 0.18 mg fluocinolone acetonide, *is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.*
- It is *designed to release fluocinolone acetonide at an initial rate of 0.25 $\mu\text{g/day}$, (b) (4) over a total period of approximately 36 months.*

2.7 Regulatory Background

- pSivida Corp submitted current NDA #210331 under the 505(b)(1) pathway.
- Right of reference letter to the approved NDA # 201923 (Iluvien) by Alimera was provided.
- YUTIQ has been submitted under IND #113140.

3 Studies Submitted

3.1 Studies Reviewed

Applicant has included a right of reference letter to NDA 201923 (by Alimera Sciences), *including, without limitation, all information and data contained therein*. The pharmacology/toxicology studies were reviewed by Dr. Conrad Chen, under NDA 201923.³ These studies included:

- A 24-Month Toxicity Study of FA/Medidur™ (Fluocinolone Acetonide Controlled Release System) Administered Via Intravitreal Injection to Pigmented Rabbits (Study JOK00002).
- 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)
- Fluocinolone Acetonide Bacterial Mutation Test (Study 961864)
- Fluocinolone Acetonide Mammalian Cell Mutation Test (Study 962441)
- Fluocinolone Acetonide Mouse Micronucleus Test (Study 961866)

The Applicant did not conduct any new nonclinical study so far.

3.2 Studies Not Reviewed

Literature references.

3.3 Previous Reviews Referenced

Nonclinical review by Dr. Aaron Ruhland, dated 5/10/2012, under IND #113140.⁴

Nonclinical review by Dr. Conrad Chen, dated 11/17/2010, under NDA 201923.⁵

³ DARRTS: NDA #201923, REV-NONCLINICAL-03(General Review), by CHEN, CONRAD H, dated 11/17/2010

⁴ DARRTS: IND #113140, REV-NONCLINICAL-03(General Review), by RUHLAND, AARON M, dated 5/10/2012

⁵ DARRTS: NDA #201923, REV-NONCLINICAL-03(General Review), by CHEN, CONRAD H, dated 11/17/2010

4 Pharmacology

4.1 Primary Pharmacology

Per label of Iluvien® (fluocinolone acetonide) intravitreal implant:⁶

Corticosteroids inhibit inflammatory responses to a variety of inciting agents including multiple inflammatory cytokines. They inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

Corticosteroids are thought to act by inhibition of phospholipase A₂ via induction of inhibitory proteins collectively called lipocortins. It is postulated that these proteins control biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting release of the common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

11 Integrated Summary and Safety Evaluation

The Applicant, EyePoint Pharmaceuticals, Inc (previously named pSivida Corp) submitted NDA 210331 under the 505(b)(1) pathway for YUTIQ™ (Fluocinolone Acetonide Intravitreal implant in applicator, 0.18 mg), to treat non-infectious uveitis affecting the posterior segment of the eye. It also submitted the proposed labeling text to comply with the “Pregnancy and Lactation Labeling Rule” (PLLR).

Applicant has the right of reference to NDA 201923 for Iluvien® (fluocinolone acetonide) intravitreal implant 0.19 mg. No issues were identified that would affect approvability.

Minor format and language changes to adhere to PLLR guidance and provide consistency of language across paragraphs in sections 8 and 13 were made to enhance readability of labeling.

12 Appendix/Attachments

Current proposed labeling text in sections 8 and 13:

⁶ <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4400e471-7402-11df-93f2-0800200c9a66>

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

(b) (4)

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2. Lactation

Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. (b) (4)

It is not known whether intravitreal treatment with **YUTIQ** could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. (b) (4)

The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for **YUTIQ** and any potential adverse effects on the breastfed child from **YUTIQ**.

8.4. Pediatric Use

Safety and effectiveness of **YUTIQ** in pediatric patients have not been established.

8.5. Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11. DESCRIPTION

12. CLINICAL PHARMACOLOGY

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 **YUTIQ**.

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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALING DONG
10/01/2018

LORI E KOTCH
10/01/2018