

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203324Orig2s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 203324/Original 2	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Photrexa Viscous, Photrexa Established/Proper Name: riboflavin Dosage Form: ophthalmic solution Strengths: 0.146% Device: KXL System		
Applicant: Avedro, Inc.		
Date of Receipt: October 16, 2015		
PDUFA Goal Date: July 15, 2016 (Major amendment received April 15, 2016, extending review clock three (3) months)		Action Goal Date (if different):
RPM: Jacquelyn Smith		
Proposed Indication(s): Treatment of corneal ectasia following refractive surgery		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
published literature	pharmacology and toxicology section of the application and labeling relied upon the published literature

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

The applicant is not relying upon a reference product.

All nonclinical safety and pharmacology data cited in the NDA are from published literature. A majority of the toxicological data (non-clinical) for riboflavin described in the literature was generated following oral administration. Topical riboflavin with concurrent exposure to UV-A light has been used for the treatment of keratoconus and corneal ectasia and both in vitro and in vivo nonclinical studies have been conducted using this methodology. The data described in the submitted literature is scientifically relevant to the proposed product because the studies used the same active pharmaceutical ingredient as contained in the Sponsor's drug product, and the doses and formulations used in the reported non-clinical studies are scientifically relevant to the proposed product.

The applicant has conducted their own corneal crosslinking clinical trials utilizing the final formulations (s) of the to-be-marketed riboflavin. Clinical information does not rely on published literature.

RELIANCE ON PUBLISHED LITERATURE

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

***(Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES NO

If “**NO**” to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR

314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

JACQUELYN E SMITH
07/18/2016

MEMORANDUM

DATE: July 13, 2016

FROM: William Maisel, MD, MPH
Deputy Director for Science, CDRH

William H. Maisel
-S

Digitally signed by William H. Maisel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=2000542400,
cn=William H. Maisel -S
Date: 2016.07.13 16:15:32 -0400'

TO: NDA 203324
Avedro Photrexa Viscous (riboflavin phosphates ophthalmic solution) 1.2 mg/mL,
20% dextran and Photrexa (riboflavin phosphates ophthalmic solution) 1.2
mg/mL KXL system (UVA Light System)

The purpose of this memo is to provide documentation of CDRH's final recommendation concerning the *Corneal Ectasia Following Refractive Surgery* indication for the above-mentioned NDA. CDRH/ODE previously recommended approval for the keratoconus indication.

In a memo dated April 13, 2016, CDRH's Office of Device Evaluation (ODE) recommended against approval of the NDA for the post-refractive corneal ectasia indication primarily related to concerns about the statistical analysis plan and ODE's conclusion that insufficient clinical data had been provided to conclude that the product is safe and effective for the post-refractive corneal ectasia population.

On June 2, 2016, Dr. Jeff Shuren, CDRH Director met with the ODE review team to discuss their recommendations concerning the post-refractive corneal ectasia indication. In addition, on June 15, 2016, Dr. Shuren and Dr. Woodcock, CDER Director, met to discuss the available evidence and to consider the differing perspectives of the CDER and CDRH review teams.

After considering the available valid scientific evidence as well as the benefits and risks of the therapy, CDRH concurs with the ODE review team that additional longer-term clinical data should be collected. However, CDRH believes that the available non-clinical and clinical data is sufficient to support marketing approval – and that longer term clinical data may be collected during a postmarket study.

This recommendation was communicated to CDER, and on July 5, 2016, Commander Brad Cunningham, Chief of ODE's Diagnostic and Surgical Devices Branch in the Division of Ophthalmic and ENT Devices Branch provided detailed specific recommendations for the product labeling. On July 12, 2016, I was provided copies of the draft labeling for the drug and the device, as well as the draft decision letter.

MEMORANDUM RE: NDA 203324

July 13,2016

Although the draft labeling does not directly address all the items identified in Commander Cunningham's email, I have reviewed the draft labeling (KXL Operator's Manual, PHOTREXA VISCOUS and PHOTREXA "Highlights of Prescribing Information" and "Full Prescribing Information") in detail and believe it represents a truthful and accurate representation of the information relied upon by the Agency to make the approval decision and concur with the contents.

In summary, based on evaluation of the scientific evidence, review of the draft labeling, and plans for post-approval study of longer-term outcomes, CDRH recommends that the NDA be APPROVED for the indication of corneal ectasia following refractive surgery.

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/s/

JACQUELYN E SMITH
07/14/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 203324
Product Name: Photrexa Viscous (riboflavin 5'-phosphate ophthalmic solution) 1.46 mg/mL with 20% dextran and Photrexa (riboflavin 5'-phosphate ophthalmic solution) 1.46 mg/mL and KXL System

PMC Description: A registry should provide a long term evaluation of the durability of the treatment effect of the procedure in at least 100 corneal crosslinking-treated subjects at 3 years with a pre-treatment diagnosis of post-refractive corneal ectasia.

PMC Schedule Milestones:	Final Protocol Submission:	<u>1/2017</u>
	Study/Trial Completion:	<u>7/2023</u>
	Final Report Submission:	<u>12/2023</u>
	Other: <u>First Enrolled Subject</u>	<u>10/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Safety and effectiveness of this drug-device combination has been demonstrated in the post-refractive corneal ectasia indication. The studies followed the effect of the procedure for one year and while this serves as an efficacious result, it is not known if the effect will persist in subsequent years. Long term durability of the procedure is not well described in the literature.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Safety and effectiveness of this drug-device combination has been demonstrated in the post-refractive corneal ectasia indication. The long term durability of the procedure is not known from the trials nor is it well described in the literature. This PMC is meant to provide data on whether the effect of corneal crosslinking (i.e., effect on subject's keratometric measures, best corrected visual acuity and intraocular pressure) are maintained for an extended period of time.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A registry should provide a long term evaluation of at least 100 corneal crosslinking -treated subjects at 3 years with a pre-treatment diagnosis of post-refractive corneal ectasia. Evaluation of these subjects would include, at a minimum, yearly examinations by qualified investigators with recording of the subjects' keratometric measurements; the subjects' best corrected visual acuity, and the subjects' intraocular pressure.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
 - Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 - There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

WILLIAM M BOYD
07/12/2016

OZLEM A BELEN
07/12/2016

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

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

Memorandum

Date: July 7, 2016

To: Jacquelyn Smith, Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Meena Ramachandra PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: PHOTREXA[®] VISCOUS (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146% for topical ophthalmic use
PHOTREXA[®] (riboflavin 5'-phosphate ophthalmic solution) 0.146% for topical ophthalmic use
NDA 203324

As requested in DTOP's consult dated November 20, 2015, OPDP has reviewed the draft PI and proposed carton and container labeling for Photrexa (riboflavin 5'-phosphate ophthalmic solution) and Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) indicated for use with the KXL System in corneal collagen cross-linking for the treatment of corneal ectasia after refractive surgery.

OPDP reviewed the proposed substantially complete version of the PI titled, "Corneal Ectasia added to April 13 2016 NDA 203324 labeling.docx" received via e-mail from Regulatory Health Project Manager Jacquelyn Smith on July 6, 2016. OPDP's has no comments on the draft PI.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

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

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/s/

MEENA RAMACHANDRA
07/07/2016

CDRH
OFFICE OF DEVICE EVALUATION
CLINICAL REVIEW

From: Maryam Mokhtarzadeh, MD DSDB/DOED/ODE

To: Bradley Cunningham, DSDB Branch Chief
Damia Jackson, Project Manager DOED
Dexiu Shi, Scientific Reviewer
Bruce Drum, Scientific Reviewer
Malvina Eydelman, DOED Division Director

Malvina B. Eydelman -S
2016.04.29 17:06:38 -0400

Re: NDA 203324 : Photrexa, Photrexa Viscous, KXL Device
riboflavin ophthalmic solution (20% dextran), riboflavin ophthalmic solution (0% dextran), UV-A Irradiation
Avedro, Inc.

Prior Clinical Reviews:

Initial Clinical Review 2/7/14
Response to Complete Response Letter Review 3/24/15
CDRH Off-the -Clock review of Post-Hoc Analyses 9/30/2015
Response to Complete Response Letter Review 1/19/2016

Proposed Indications for Use:

- For the treatment of corneal ectasia following refractive surgery

Date: April 28, 2016

Recommendation: Not Approvable (Complete Response). As recommended in my last review: “A new clinical study is needed to support approval with 1) more clearly defined diagnostic and historical support for the iatrogenic disease studied as well as 2) improved methodology for collection of both safety and effectiveness data to reduce uncertainty with regard to adverse events and stability of benefit achieved, and 3) an appropriate study design to allow meaningful analysis of observed measurements rather than reliance on LOCF.”

Introduction:

Per the cover letter, “Included in this submission is information from the literature to support the progressive nature of corneal ectasia following refractive surgery.”

History of the file:

I provided an initial review on February 7, 2014 for this NDA prior to a Complete Response action taken by CDER. Avedro’s official response to the Complete Response letter was received by the agency September 29, 2014. The joint advisory committee met on February 24, 2015. A second complete response letter was subsequently sent to the sponsor followed by months of interaction with the sponsor and off-the-clock review. The sponsor responded to the second complete response letter on October 15, 2015 leading to CDER’s decision to split the application in 4/2016 according to indication

with an approval for the progressive keratoconus indication on 4/16/2016 and submission of new data (literature) for the postrefractive corneal ectasia indication which is reviewed below.

Literature

The sponsor's summary of the literature is cut and paste below:

Corneal ectasia is a group of non-inflammatory syndromes characterized by progressive corneal steepening and thinning. The American Academy of Ophthalmology Corneal Ectasia Preferred Practice Pattern Guideline (AAO 2013) includes post-surgical corneal ectasias, such as those occurring after LASIK or PRK, as part of this group of corneal disorders defined by their progressive nature. Although post-surgical corneal ectasia has been recognized as an uncommon complication of LASIK and other refractive surgical procedures, its etiology, natural history, and rate of progression are not well documented in published literature via prospective studies. Retrospective studies of post-LASIK corneal ectasia document progressive topographic steepening and corneal thinning, decreasing visual acuity, and unstable refraction. (Randleman 2003, Rad 2004, Spadea 2012). Some authors prefer the term “progressive post-LASIK keratectasia” (PPLK) for the condition as it is thought to best represent the etiology and natural history of the disorder (Rad 2004). Documentation of progression has been reported in a study that looked at the effect of corneal crosslinking in eyes with post-LASIK corneal ectasia (Hafezi 2007).

Reviewer Comment: Note that the sponsor confirms that the “...etiology, natural history, and rate of progression [of post-surgical corneal ectasia] are not well documented in published literature via prospective studies....” This is a critical point and underscores the difficulty of accepting assumptions necessary to support use of LOCF for almost the entirety of the control arm at the time of endpoint analyses in the pivotal studies.

Specific comments on the five literature references included in the current submission appear below.

1. Randleman JB, Russell B, Ward MA, Thompson KP, Stulting RD. Risk factors and prognosis for corneal ectasia after LASIK. *Ophthalmology*. 2003 Feb;110(2):267-75.

Abstract:

Purpose: To review cases of corneal ectasia after laser in situ keratomileusis (LASIK), identify preoperative risk factors, and evaluate methods and success rates of visual rehabilitation for these cases.

Design: Retrospective nonrandomized comparative trial.

Participants: Ten eyes from seven patients identified as developing corneal ectasia after LASIK, 33 previously reported ectasia cases, and two control groups with uneventful LASIK and normal postoperative courses: 100 consecutive cases (first control group), and 100 consecutive cases with high myopia (≥ 8 diopters [D]) preoperatively (second control group).

Methods: Retrospective review of preoperative and postoperative data for each case compared with that of previously reported cases and cases with uneventful postoperative courses.

Main Outcome Measures: Preoperative refraction, topographic features, residual stromal bed thickness (RSB), time to the development of ectasia, number of enhancements, final best-corrected visual acuity (BCVA), and method of final correction.

Results: Length of follow-up averaged 23.4 months (range, 6–48 months) after LASIK. Mean time to the development of ectasia averaged 16.3 months (range, 1–45 months). Preoperative refraction averaged

-8.69 D compared with -5.37 D for the first control group ($P = 0.005$). Preoperatively, 88% of ectasia cases met criteria for forme fruste keratoconus, compared with 2% of the first control group ($P = 0.0000001$) and 4% of the second control group ($P = 0.0000001$). Seven eyes (70%) had RSB $< 250 \mu\text{m}$, as did 16% of eyes in the first control group and 46% of the second control group. The mean RSB for ectasia cases ($222.8 \mu\text{m}$) was significantly less than that for the first control group ($293.6 \mu\text{m}$, $P = 0.0004$) and the second control group ($256.5 \mu\text{m}$; $P = 0.04$). Seven eyes (70%) had enhancements. Only 10% of eyes lost more than one line of BCVA, and all patients eventually achieved corrected vision of 20/30 or better. One case required penetrating keratoplasty (10%), while all others required rigid gas-permeable contact lenses for correction.

Conclusions: Significant risk factors for the development of ectasia after LASIK include high myopia, forme fruste keratoconus, and low RSB. All patients had at least one risk factor other than high myopia, and significant differences remained even when controlling for myopia. Multiple enhancements were common among affected cases, but their causative role remains unknown. We did not identify any patients who developed ectasia without recognizable preoperative risk factors.

- a. Sponsor highlighted the following: "Postoperative topographies were available on all patients. These documented the progression of ectasia over time. Most cases of ectasia became apparent within the first 6 months after surgery (Fig 8); however, some eyes developed delayed-onset ectasia. In fact, one patient maintained a relatively stable topography and acuity for more than 4 years before the onset of ectasia. Refractions shifted dramatically during the postoperative period (Table 4)."

Reviewer Comment: Based on Table 2 all but 2/11 eyes reported had forme fruste keratoconus preoperatively. These subjects may be representing native disease progression rather than predominantly iatrogenic disease.

- b. "Most patients were successfully fit with rigid gas-permeable (RGP) contact lenses postoperatively, and only one eye required penetrating keratoplasty for visual rehabilitation (Fig 10)."
- c. "As in any retrospective study, inherent problems limit the applicability of these results to the general population.... In addition, the referral of all patients included in this study to the contact lens service at a tertiary care institution may have created a bias toward the inclusion of patients amenable to contact lens fitting and motivated to pursue this alternative."

2. Rad AS, Jabbarvand M, Saifi N. Progressive keratectasia after laser in situ keratomileusis. J Refract Surg. 2004 Sep-Oct;20(5 Suppl):S718-22.

Abstract:

PURPOSE: We describe ten patients who developed progressive keratectasia following laser in situ keratomileusis (LASIK) and identify possible factors that may lead to ectasia.

METHODS: In this retrospective study, we reviewed the files of 3,634 patients (6941 eyes) who had LASIK between March 2000 and April 2003. Ten patients (14 eyes, 0.2%) developed progressive keratectasia. We also evaluated consequent therapeutic measures and final visual status of these patients.

RESULTS: Patients were examined at a mean 24.9 ± 8.1 months after LASIK. Ectasia developed within a mean 14 ± 0.3 months after surgery. At baseline, mean keratometric power was 44.7 ± 2.30 D, mean corneal thickness was 516 ± 18.9 pm, and mean attempted correction was -10.85 ± 3.20 D.

We found a statistically significant correlation between residual stromal thickness, attempted correction; and occurrence of progressive keratectasia. We also found that preexisting abnormal corneal topography was a risk factor for progressive keratectasia. Ultimately, most patients had reasonable visual acuity after penetrating keratoplasty.

CONCLUSION: Progressive keratectasia is a vision threatening complication of LASIK that may occur in previously healthy or diseased eyes. The most important risk factors are residual stromal thickness and preexisting abnormal corneal topography. Penetrating keratoplasty may be a reasonable therapeutic measure for severe cases of progressive keratectasia.

- a. "This disorder has several names, including but not limited to LASIK-induced corneal ectasia, postLASIK keratectasia, iatrogenic keratectasia, iatrogenic keratoconus, and progressive post-LASIK keratectasia (PPLK). We prefer progressive keratectasia after LASIK, as the phrase defines the etiology, natural history, and pathology of the disorder."
 - b. "Progressive keratectasia was diagnosed by decreasing visual acuity, unstable refraction, pro-gressive topographic steepening, (≥ 1.00 diopter [D] for each 6-month period of follow-up), and corneal thinning (≥ 20 μm for each 6-month period of follow-up).
 - c. "Corneal steepening occurred centrally in eight eyes (57.2%) and inferiorly in six eyes (42.8%) (Table 2). In all but one of the inferior steepening eyes, there were previous corneal risk factors including decreased corneal thickness, high keratometric power, and abnormal topographic patterns. The mean preoperative corneal thickness of the central steepening group was 526.2 ± 13.9 μm and in the inferior steepening group, 503.1 ± 17.3 μm . Of eight central steepening cases, only one (12.5%) had abnormal topography, but five of six (83.3%) inferior steepening cases had abnormal topography. There was a statistically significant difference between the central and inferior steepening groups in pre-existing topographic abnormalities ($P=.02$) and corneal thickness ($P=.01$). Seven patients eventually underwent penetrating keratoplasty..."
 - d. "Pre-existing corneal pathology. We found corneal risk factors including low pachymetry measurements, abnormal corneal topography, and high keratometric power in 6 of 14 eyes (43%). These risk factors were found in only one of eight central steepening cases and in all but one in the inferior steepening group. This is similar to the findings reported by Faraj and colleagues, who suggested that progressive keratectasia after LASIK in normal eyes presents as central steepening, and as inferior steepening in eyes that had preoperative pathology such as keratoconus or forme fruste keratoconus. 19 Regarding these data, we suggest dividing cases of progressive keratectasia after LASIK into two subgroups: with central steepening and no previous corneal risk factors, and with inferior steepening and previous corneal risk factors. Additional study is required to confirm this hypothesis."
3. Hafezi F, Kanellopoulos J, Wiltfang R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. *J Cataract Refract Surg.* 2007 Dec;33(12):2035-40.

Abstract:

PURPOSE: To determine whether riboflavin and ultraviolet-A (UVA) corneal crosslinking can be used as an alternative therapy to prevent the progression of keratectasia.

SETTING: Institute for Refractive and Ophthalmic Surgery, Zurich, Switzerland, and a private clinic,

Athens, Greece.

METHODS: Corneal crosslinking was performed in 10 patients with formerly undiagnosed forme fruste keratoconus or pellucid marginal corneal degeneration who had laser in situ keratomileusis (LASIK) for myopic astigmatism and subsequently developed iatrogenic keratectasia. Surgery was performed in 1 eye per patient.

RESULTS: Crosslinking induced by riboflavin and UVA arrested and/or partially reversed keratectasia over a postoperative follow-up of up to 25 months as demonstrated by preoperative and postoperative corneal topography and a reduction in maximum keratometric readings.

CONCLUSION: Riboflavin–UVA corneal crosslinking increased the biomechanical stability of the cornea and may thus be a therapeutic means to arrest and partially reverse the progression of LASIK-induced iatrogenic keratectasia.

Reviewer Comment: The abstract quote above implies that these subjects may not have had a normal topography in the past and the “probable reason[s]” cited in Table 1 imply pre-existing noniatrogenic ectatic disease. Therefore, this population does not necessarily represent iatrogenic ectasia as opposed to pre-existing ectasia post-refractive surgery.

- a. “Affected eyes have progressive central or inferior corneal steepening associated with stromal thinning and significant changes in refractive error.”

Reviewer Comment: Structural changes in iatrogenic ectasia may not occur in the same corneal location as keratoconus or other ectatic etiologies.

- b. “Our results show that riboflavin–UVA corneal crosslinking can arrest and, in some cases, partially reverse otherwise progressive iatrogenic keratectasia after LASIK.... Four of the 10 eyes gained more than 2 lines in the BSCVA. The cause of this optical regularization is unknown.”

Reviewer Comment: Improvement was captured in subjects, however, given that this population potentially represented pre-existing ectatic disease, it is unclear whether the improvement is due to treatment of the underlying natural disease or the biomechanical changes induced iatrogenically.

- c. “Metalloproteinases and other enzymes involved in inflammatory processes may play a role in the pathogenesis of keratoconus.¹⁵ It has not been shown that these components also play a role in iatrogenic keratectasia. One might speculate that crosslinking induced inflammation, including enzymatic degradation of collagen, leads to deterioration. On the other hand, Spoerl et al.¹⁶ report that crosslinked collagen is significantly more resistant to enzymatic degradation than native corneal collagen. Perhaps the biochemical stabilization of collagen by crosslinking contributes to the effect.”

Reviewer Comment: Further support that iatrogenic ectasia may have distinct considerations/behavior when compared to naturally occurring corneal ectatic disease and iatrogenic disease merits independent consideration for approval of a distinct IFU.

4. Spadea L, Cantera E, Cortes M, Conocchia NE, Stewart CW. Corneal ectasia after myopic laser in situ keratomileusis: a long-term study. Clin Ophthalmol. 2012;6:1801-13.

Abstract:

Background: The purpose of this study was to evaluate the long-term postoperative incidence of and key factors in the genesis of corneal ectasia after myopic laser-assisted in situ keratomileusis (LASIK) in a large number of cases.

Methods: A retrospective review of one surgeon's myopic LASIK database was performed. Patients were stratified into two groups based on date of surgery, ie, group 1 (1313 eyes) from 1999 to 2001 and group 2 (2714 eyes) from 2001 to 2003. Visual acuity, refraction, pachymetry, and corneal topography data were available for each patient from examinations performed both before and after the refractive procedures. **Results:** Of the 4027 surgically treated eyes, 23 (0.57%) developed keratectasia during the follow-up period, which was a minimum seven years; nine eyes (0.69%) were from group 1 and 14 eyes (0.51%) were from group 2. The onset of corneal ectasia was at 2.57 ± 1.04 (range 1–4) years and 2.64 ± 1.29 (range 0.5–5) years, respectively, for groups 1 and 2. The most important preoperative risk factors using the Randleman Ectasia Risk Score System were manifest refractive spherical error in group 1 and a thin residual stromal bed in group 2. Each of the cases that developed corneal ectasia had risk factors that were identified.

Conclusion: Ectasia was an uncommon outcome after an otherwise uncomplicated laser in situ keratomileusis procedure. The variables present in eyes developing postoperative LASIK ectasia can be better understood using the Randleman Ectasia Risk Score System.

Reviewer Comments:

1. *Note that this publication specifies a subset of postrefractive corneal ectasia subjects and therefore may not be applicable to the entire population targeted by the IFU proposed by the sponsor.*
2. *Note that this is a publication from a single surgeon's database which may provide a more homogeneous population than the one represented in the pivotal studies and may have limited applicability to the general post-refractive population in the US. This is an important point given that a critical issue on this file has been the lack of diagnostic criteria defining the disease and the fact that different clinicians may have unique diagnostic criteria they are using.*
 - a. "The onset of corneal ectasia was at 2.57 ± 1.04 (range 1–4) years and 2.64 ± 1.29 (range 0.5–5) years, respectively, for groups 1 and 2."
Reviewer Comment: Note that history of refractive surgery for subjects in the pivotal trial ranged up to 13 years prior to enrollment.
 - b. "In most cases, this keratectasia was characterized by progressive steepening of corneal curvature inferiorly or centrally, progressive and significant increases in myopia, with or without increasing astigmatism, an associated severe decrease in uncorrected and often best-corrected visual acuity, and a progressive thinning of the cornea..."
Reviewer Comment: This language was highlighted by the sponsor for our review. Note that the quote begins "In most cases..." – "most" is not all and therefore these data do not support that all postrefractive corneal ectasia is progressive nor that LOCF is appropriate to use for almost the entirety of the control arm.
 - c. While progression is described in some subjects, not all subjects progressed to requiring penetrating keratoplasty as some were managed with spectacles and/or hard contact lenses. Therefore, the critical information that was not captured was whether the ectasia stabilized in any subjects and/or what range was captured in the rate of progression across the population.
 - d. "In the present study, patient data are limited to surgeries performed up to 2003, when the risk of post-LASIK ectasia was not widely known and higher corrections were attempted. Therefore, our conclusions do not necessarily apply to current practice."

Reviewer Comment: This is certainly a limitation as the population (and data) described in this submission are likely dated due to advances in clinical practice.

- e. "One of the most common findings in ectasia cases has been abnormal preoperative topography, suggesting a pre-existing ectatic corneal disorder, eg, keratoconus, forme fruste keratoconus, or pellucid marginal degeneration.^{5,8,41,42}"

Reviewer Comment: This fact stresses the underlying problem that without clear diagnostic criteria including preoperative topography data, a postrefractive corneal ectasia population cannot be distinguished from other forms of ectasia (such as keratoconus) and a separate IFU cannot be justified accordingly.

- f. "...post-LASIK ectasia in a normal cornea commonly presents as a central steepening, whereas corneas with forme fruste keratoconus are more likely to develop inferior ectasia. Thus, occurrence of inferior ectasia in these patients could suggest preoperative existence of forme fruste keratoconus."

Reviewer Comment: This article references other literature supporting structural differences within the general "postrefractive corneal ectasia" population depending on the etiology/history of the abnormality. This information is consistent with my recommendations that diagnostic criteria and historical information are critical when discussing this population in order to support a clear IFU. Device treatment parameters may not be appropriate across the range of structural/anatomic differences which could be captured across these disease processes. For example, centration of the beam with respect to the limbus and small treatment diameters may not be appropriate in post-LASIK or iatrogenic ectasia (consistent with trends in data from the pivotal trial indicating that larger diameters may have been more effective for the postrefractive corneal ectasia population than the progressive keratoconus population). Rather decentered treatments may be necessary. While this may appear to be an effectiveness issue it also potentially impacts device safety.

5. American Academy of Ophthalmology. Preferred Practice Pattern: Corneal Ectasia. 2013.

"CLINICAL OBJECTIVES

- Identify corneal ectasia risk factors and associated conditions, and recognize signs in the clinical examination
- Establish the diagnosis of corneal ectasia, including use of appropriate diagnostic technologies
- Understand appropriate surgical and non-surgical treatment options
- Improve visual function
- Prevent loss of visual function
- Educate and involve the patient in the management of this disease"

- a. "Corneal ectasia is usually bilateral, and it varies in severity and progression."
- b. "Though not currently approved by the U.S. Food and Drug Administration (FDA), collagen cross-linking has the potential to reduce the risk of progressive ectasia (particularly in its early stages) and stabilize the corneal contour. This is the case particularly in mild to moderate keratoconus, and it may also hold promise in cases of corneal ectasia occurring after keratorefractive surgery."
- c. "Corneal ectasia can occur shortly after LASIK and photorefractive keratectomy (PRK) in eyes that had pre-existing forme fruste keratoconus or years later in eyes that had no preoperative signs of keratoconus."

Reviewer Comment: This publication describes multiple corneal ectasias, not limited to postrefractive corneal ectasia. No treatment data is presented with the KXL system in support of a postrefractive corneal ectasia indication. While acknowledging that progression can occur, this publication does not provide support for LOCF for all subjects with this disease nor evidence that all patients progress (i.e., ultimately require corneal transplant).

Conclusion: While corneal crosslinking is a promising treatment for patients with iatrogenic ectatic disease, the lack of prospective natural history data on a well-defined population remains a limitation in supporting an IFU based on the flawed pivotal studies presented in this NDA. No data has been presented describing outcomes of this population with the KXL system (device and treatment parameters proposed for marketing). The literature provided in the current submission does not address my previously stated concerns. Please refer to my Clinical Review from 1/19/2016 for a detailed discussion regarding my outstanding concerns and rationale for my consistent recommendation below:

Recommendation: Not Approvable (Complete Response) recommended for the post-refractive corneal ectasia indication. A new clinical study is needed to support approval with 1) more clearly defined diagnostic and historical support for the iatrogenic disease studied as well as 2) improved methodology for collection of both safety and effectiveness data to reduce uncertainty with regard to adverse events and stability of benefit achieved, and 3) an appropriate study design to allow meaningful analysis of observed measurements rather than reliance on LOCF.

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/s/

JACQUELYN E SMITH
04/29/2016