CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203324Orig2s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review for NDA 203324
Review #2

Date	July14, 2016
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	203324
Applicant	Avedro, Inc.
Date of Resubmission	October 16, 2015
PDUFA Goal Date	July 15, 2016
505(b)(2)	Yes
Proprietary Name / Established (USAN) names	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
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	NDA 303324-1: treatment of progressive keratoconus (Approved) NDA 303324-2: treatment of corneal ectasia following refractive surgery (Pending)
Recommended:	Recommended for Approval

1. Introduction

Corneal ectasia is a well-described complication of refractive surgery, including laser in-situ keratomileusis (LASIK) and photorefractive keratectomy (PRK). It is a condition similar to keratoconus, but occurs postoperatively. Ectasia may result from unrecognized preoperative keratoconus or, less frequently, from the surgery itself. Similar to keratoconus, postoperative corneal ectasia is characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of both uncorrected visual acuity (UCVA) and BCVA.

The goal of corneal collagen cross-linking (CXL) is to biomechanically stabilize the weak cornea in keratoconus and postoperative corneal ectasia and decrease the clinical progression of these diseases. In the crosslinking procedure, riboflavin is administered topically to the eye (typically one drop every 2 minutes for 30 minutes). After riboflavin saturation through the corneal stroma, exposure to ultraviolet A (UVA) light (365 (b) (4) nm; 3 (b) (4) mW/cm^2 irradiation; (b) (4) 30 minutes' duration) induces crosslinking.

Avedro's riboflavin ophthalmic solution/UVA irradiation is a combination product consisting of a UVA 365 nm wavelength light source and riboflavin administered in conjunction with the UVA light as a photoenhancer.

Normally an iso-osmotic riboflavin ophthalmic solution is used. However, if corneal thickness is <400 µm, a (b) (4) riboflavin ophthalmic solution such as one without dextran is used until the corneal thickness is at least 400 µm.

For additional introductory detail, see the CDER Medical Officer's reviews dated 3/7/14 and 3/24/15 and the CDER CDTL reviews dated 3/10/14, 3/27/15, and 4/14/16.

2. Background

See the CDER CDTL review in DARRTS dated 4/14/16.

This is a combination product submitted under NDA 203324, which was studied under two INDs. The Office of Combination Products, in response to a Request for Designation, designated that CDER was the lead Center for this combination product under RFD070013.

The NDA was administratively split into two applications based on the submitted indications. NDA 203324-1 was designated as the NDA for the treatment of keratoconus. It was approved 4/15/16. NDA 203324-2 was designated as the NDA for the treatment of corneal ectasia following refractive surgery.

CDER/DTOP had recommended approval for NDA 203324-2 for the treatment of corneal ectasia following refractive surgery.

As described in the April 13, 2016, memorandum from William Maisel, MD, MPH, Acting Director of the Office of Device Evaluation and Malvina Eydelman, MD, Director of the Division of Ophthalmic and Ear, Nose and Throat Devices, The Center for Devices and Radiologic Health/Office of Device Evaluation (CDRH/ODE) believed that the information that has been provided in the submission was sufficient to resolve the outstanding device-related issues for the progressive keratoconus indication. However, unlike the keratoconus indication, CDRH/ODE did not believe the information provided in the submission and the available valid scientific evidence is sufficient to resolve the device-related issues or to conclude that the product is safe and effective for the post-refractive corneal ectasia population.

Based on the disagreement between the Review Divisions in CDER and CDRH on the approval of the treatment of corneal ectasia following refractive surgery, the Division of Transplant and Ophthalmology will forwarded the two conflicting recommendations through the Office/Center for resolution.

A decisional Briefing was held internally on June 8, 2016, with Janet Woodcock, CDER Center Director. The meeting included representatives from the Office of Antimicrobial Products, Division of Transplant and Ophthalmology Products; Office of Biostatistics, and Office of Biometrics IV. Dr. Woodcock agreed to meet with CDRH to discuss the approvability of the ectasia indication.

Dr. Woodcock and Dr. Jeff Shuren (CDRH Center Director) discussed this issue on June 15, 2016. Per an email from Dr. Woodcock sent Wednesday, June 15, 2016, at 6:41 PM, to John Jenkins, M.D. , Edward Cox M.D. , Renata Albrecht M.D. , and Wiley Chambers M.D., CDRH was willing to go along with approval of the indication with several requests: post market follow-up (perhaps registry) to determine longer-term fate of the corneas and patient experience; put in labelling the issues about the

laser settings and other device issues. (b) (4)

An internal meeting was held with representatives from DTOP and DSDB/DOED/ODE on June 30, 2016. DSDB/DOED/ODE committed to provide an email with suggested labeling revisions for the treatment of corneal ectasia following refractive surgery indication but stated than an additional formal review from DSDB/DOED/ODE would not be forthcoming.

In an email from Bradley Cunningham, MSE, RAC, Chief, Diagnostic and Surgical Devices Branch, Division of Ophthalmic and ENT Devices, Office of Device Evaluation, Center for Devices and Radiological Health addressed to Wiley Chambers, M.D., and Renata Albrecht, M.D., dated July 05, 2016, DSDB/DOED/ODE did not provide edits to the proposed labeling for the drug or device. There was no specific information that DSDB/DOED/ODE recommended adding in the labeling regarding the "settings" for the UV light device.

In his July 13, 2016, memorandum, William Maisel, MD, MPH, Deputy Director for Science, CDRH summarizes that based on evaluation of the scientific evidence, review of the draft labeling, and plans for a post-approval study of longer-term outcomes, CDRH recommends that the NDA be approved for the indication of corneal ectasia following refractive surgery. Dr. Maisel recommended adding a statement in the Device manual to match the drug package insert concerning the minimum age where safety and efficacy had been established (i.e., 14 years of age).

3. Labeling

The Office of Prescription Drug Promotion (OPDP) completed a review dated 7/7/2016 in DARRTS. OPDP had no additional comments on the draft PI.

The labeling for NDA 203324, 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, has been revised consistent with recommendations provided by the Agency. The labeling submitted 7/13/2016 is acceptable with the addition of the minimum age statement. See Appendix of this review for attached labeling

4. Recommendations/Risk Benefit Assessment

CDER/DTOP RECOMMENDED REGULATORY ACTION:
NDA 203324, 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, is recommended for approval for the treatment of for the treatment of corneal ectasia following refractive surgery.

RISK BENEFIT ASSESSMENT:
There is currently no FDA-approved medical therapy available in the United States (US) for the treatment of corneal ectasia following refractive surgery. For both keratoconus and corneal ectasia, early intervention usually involves the use of spectacle correction. As corneal protrusion and irregular astigmatism progress, spectacles can no longer adequately correct vision, and the use of rigid, scleral, or

hybrid contact lenses is needed to address the optical irregularity of the cornea. Corneal transplantation is the only option available when functional vision can no longer be achieved.

Corneal transplantation is not without risk – postoperative complications include transplant failure, rejection, secondary cataract, secondary glaucoma, and recurrence of keratoconus in the transplanted graft.

The applicant has submitted two adequate and well controlled trials for the corneal ectasia (UVX-001 and UVX-003) indication; these trials demonstrate statistical significance between groups at Month 3 and Month 12 favoring the CXL treatment for the indications.

While the device used in the clinical trial was not the same as the device proposed to be marketed, the KXL and UVX devices are equivalent based on the Equivalence Testing Results provided.

The most common adverse events for both the keratoconus and corneal ectasia indications occurring at 10% to 92% in UVX-001, -002, and -003 were corneal epithelium defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequelae following the corneal epithelial debridement which accompanied the procedure.

In the opinion of the CDER CDTL, the applicant has satisfactorily addressed all of the items cited in the Complete Response letter dated March 29, 2015, as approvability issues.

The benefits of the CXL procedure are considered to outweigh the risks for both indications.

CDER Clinical, Pharmacology/Toxicology, Clinical Pharmacology, CMC, Product Quality Microbiology, and Biostatistics and have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
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. A PMC 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 is recommended.

This clinical trial or 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. The action letter is recommended to include the following language:

POST MARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3106-1

A registry to provide 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.

The timetable you submitted on 7/13/2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2017
Enroll First Subject	10/2017
Study Completion:	07/2023
Final Report Submission:	12/2023

Submit clinical protocols to your IND 77,882 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

14. Administrative Action

NDA 203324, 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, is recommended for approval for the treatment of keratoconus and for the treatment of corneal ectasia following refractive surgery**.**

Appendix

The labeling for NDA 203324, 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, has been revised consistent with recommendations provided by the Agency. The labeling submitted 7/13/2016 is acceptable with the addition of the minimum age statement to the Device manual.

Note: Photrexa Viscous (riboflavin phosphates ophthalmic solution) 1.46 mg/mL 20% dextran and Photrexa (riboflavin phosphates ophthalmic solution) 1.46 mg/mL are provided in a bulk pack of 10 (ten), single-use foil pouches. Each foil pouch contains a 3 mL glass syringe of Photrexa Viscous or Photrexa contained within a Tyvek pouch.

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

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

/s/

WILLIAM M BOYD
07/14/2016

WILEY A CHAMBERS
07/15/2016