CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203324Orig2s000

CLINICAL REVIEW(S)

Deputy Division Director Review for NDA 203324

Date	July 15, 2016
From	Wiley A. Chambers, M.D.
NDA	203324
Applicant	Avedro, Inc.
Date of Resubmission	October 16, 2015
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 (Current action)
Recommended:	Recommended for Approval

1. Introduction

Keratoconus is an ocular condition characterized by progressive thinning and steepening of the central cornea, resulting in corneal optical irregularities with increasing myopia, irregular astigmatism, and consequential loss of best corrected visual acuity (BCVA).

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.
There are currently limited FDA-approved treatments in the United States (US) for corneal ectasia following refractive surgery. Corneal transplantation is the only option available when functional vision can no longer be achieved.

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.

2. Background

General Regulatory Background
This NDA application was originally submitted with a request for two indications (treatment of progressive keratoconus and treatment of ectasia following refractive surgery). The application was administratively split based on the indications and the combination product was approved for the treatment of patients with progressive keratoconus on April 15, 2016.

Combination Product
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.

Drug Constituent- Riboflavin
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 contain riboflavin 5'-phosphate sodium, sodium chloride, sodium phosphate monobasic, sodium phosphate dibasic, and sterile water for injection. Photrexa Viscous contains 20% dextran 500 and Photrexa does not.

Device Constituent- KXL System
The KXL System is an electronic medical device that delivers ultraviolet light (365 nm wavelength) in a circular pattern onto the cornea after application of Photrexa or Photrexa Viscous (riboflavin ophthalmic solution). UVA flux and irradiation time at the cornea are controlled by an onboard computer system.

3. Product Quality

DRUG PRODUCT COMPOSITION

Each mL contains:

Ingredient	Photrexa Viscous	Photrexa	Function
Riboflavin 5'-Phosphate Sodium, USP	1.53 mg	1.53 mg	Active
Dextran 500			(b) (4)
Sodium chloride, USP			
Sodium phosphate, monobasic, USP			
Sodium phosphate, dibasic, USP			
Sterile water for injection, USP			

*1.53% riboflavin 5'-phosphate sodium is equal to 0.146% riboflavin 5'-phosphate and equal to 0.120% riboflavin.

Container Closure System for Photrexa and Photrexa Viscous

Syringe Barrel (b) (4)

Plunger Stopper (b) (4)

Plunger Rod (b) (4)

QUALITY CONTROL DRUG PRODUCT SPECIFICATIONS

The quality control specifications for both riboflavin ophthalmic solutions, Photrexa Viscous (riboflavin ophthalmic solution) 20% dextran and Photrexa (riboflavin ophthalmic solution) 0% dextran, are provided in the table below.

Table 1: Drug Product Specifications

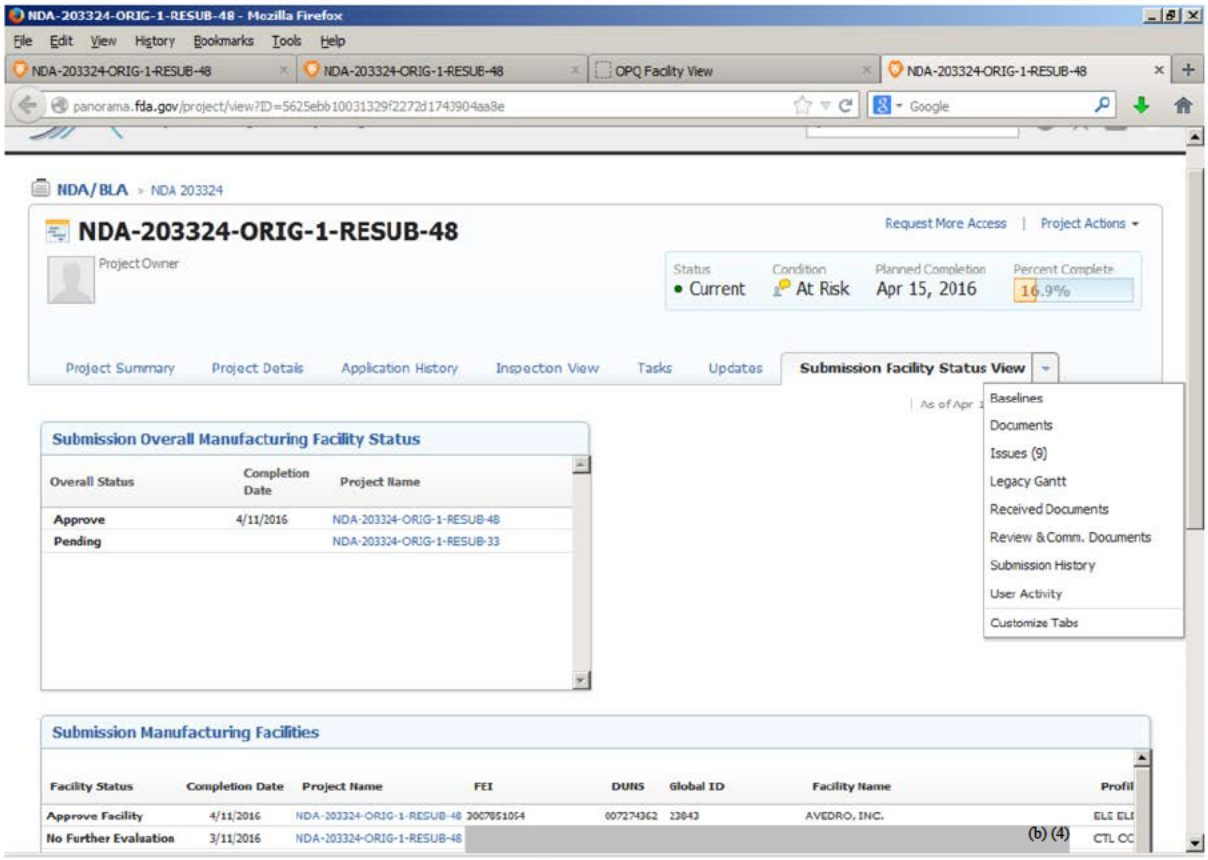
Test Description	Method	Acceptance Criteria
Appearance	Visual	A glass syringe containing a clear yellow solution, no visible particulates, and no leakage. May contain a minimal bubble
Identification	RP-HPLC	Retention time ((b) (4) %) and UV spectra conform
Assay	RP-HPLC	(b) (4) % LC (b) (4) mg/ml)
Riboflavin 5'-monophosphate	RP-HPLC	Not less than (b) (4) % Relative Area
pH	USP <791>	(b) (4)
Sterility	USP <71>	No Growth
Viscosity	USP <911>	Photrexa: (b) (4) cP Photrexa (b) (4) cP
Osmolality	USP <785>	Photrexa: (b) (4) mOsm/kg Photrexa (b) (4) mOsm/kg
Particulate Matter	USP <789>	(b) (4) particles/mL (b) (4) particles/mL particles/mL
Endotoxin	USP <85>	(b) (4) EU/mL
Degradants	RP-HPLC	Specified: (b) (4) RRT (b) (4) % RRT % RRT % Each Unspecified: (b) (4) % Total (b) (4) %

See Chemistry review dated 4/13/16.

This NDA is recommended for approval from the CMC perspective. All CMC issues concerning the drug substance and the drug products have been satisfactorily resolved. An overall recommendation of Acceptable has been made by the Office of Compliance.

FACILITIES

An overall recommendation of Acceptable has been made by the Office of Compliance.



4. Nonclinical Pharmacology/Toxicology

See original Pharmacology/Toxicology review dated 2/26/2014. The applicant has submitted NDA 203324 as a 505(b)(2) application and relies on published nonclinical data to support this application. All nonclinical safety and pharmacology data cited in the NDA are from published, publicly available research articles. Under the conditions used for corneal collagen cross-linking, riboflavin functions as a photoenhancer. The application was considered approvable from a Pharmacology/Toxicology perspective during an earlier review cycle and no additional nonclinical information has been submitted to alter that conclusion.

5. Clinical Pharmacology/Biopharmaceutics

NDA 203-324 has been reviewed by the Clinical Pharmacology review team. The application was considered approvable from a Clinical Pharmacology perspective during an earlier review cycle and no additional information has been submitted to alter that conclusion.

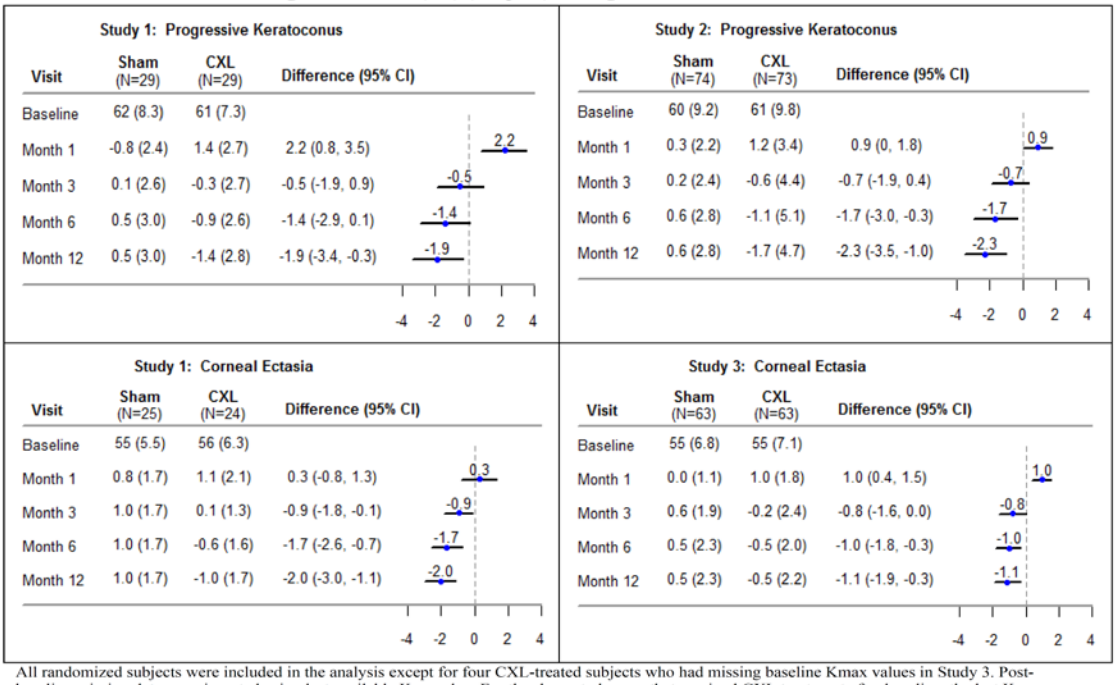
There were no pharmacokinetic studies conducted to determine the actual systemic exposures to riboflavin following topical ocular instillation of the 0.12% riboflavin ophthalmic solutions during one-time corneal collagen crosslinking treatment.

Assuming 100% bioavailability of riboflavin following topical ocular instillation of the proposed 0.12% riboflavin eye drops, the average systemic exposure to riboflavin during one-time CCXL treatment of one eye in the 12-month UVX trials would not exceed (b) (4) mg, which is below the Joint FAO/WHO Expert Committee on Food Additives upper limit of acceptable oral daily intake of riboflavin (35 mg for a 70 kg person).

6. Clinical/Statistical – Efficacy

The applicant has submitted two adequate and well controlled trials for both the keratoconus (UVX-001 and UVX-002) and corneal ectasia (UVX-001 and UVX-003) indications; these trials demonstrate statistical significance between groups at Month12 favoring the CXL treatment for both indications as shown below.

Figure 1: Mean (SD) (Diopter) Change from Baseline Kmax



All randomized subjects were included in the analysis except for four CXL-treated subjects who had missing baseline Kmax values in Study 3. Post-baseline missing data were imputed using last available K_{max} value. For the sham study eyes that received CXL treatment after baseline, the last K_{max} measurement recorded prior to receiving CXL treatment was used in the analysis for later time points.

7. Safety

In corneal ectasia subjects, the most common ocular adverse reactions were corneal opacity (haze), corneal epithelium defect, corneal striae, dry eye, eye pain, punctate keratitis, photophobia, reduced visual acuity, and blurred vision. These events are expected sequelae following epithelial corneal debridement and occurred at a higher incidence than observed in control subjects, who did not undergo debridement or exposure to UVA light.

Adverse events reported in non-study, non-randomized CXL treated were similar in in terms of preferred terms and frequency to those seen in randomized study eyes.

For additional safety details, 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 4/15/16.

8. Regulatory Briefing/Advisory Committee Meeting

A Regulatory Briefing was held on Friday, March 20, 2015. For additional details, see the CDER CDTL review 3/27/15.

A joint meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) and the Ophthalmic Devices Panel of the Medical Devices Advisory Committee (OP-MDAC) was held on February 24, 2015. For additional details, see the CDER CDTL review 3/27/15.

9. Pediatrics

Submission of a pediatric assessment was not required because the application is for an orphan-designated indication.

For additional pediatric details, 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 4/15/16.

10. Other Relevant Regulatory Issues

CDRH

During the review of this application, CDRH has expressed concern about the design and conduct of the clinical trials which were submitted in support of the treatment of ectasia following refractive surgery. These concerns have been noted in prior reviews. 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. In addition, CDER concurred with CDRH's recommendation that the statement, "The safety and effectiveness of corneal collagen cross-linking has not been established in pediatric patients below the age of 14" which is currently in the package insert of the drug product, also be placed in the Device Operator's Manual.

SEALD

A Study Endpoints and Labeling Development (SEALD) consult request was made by the Division of Transplant and Ophthalmology Products (DTOP) for NDA 203324 on 2/12/15.

For additional details, see the CDER CDTL review 3/27/15.

FINANCIAL DISCLOSURE

See the original Medical Officer's review dated 3/7/2014. No issues precluding approval were identified.

OSI

A routine Office of Scientific Investigations (OSI) audit was requested. See the original Medical Officer's review dated 3/7/2014. No issues of data integrity were identified.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) issued a PROPRIETARY NAME REQUEST CONDITIONALLY ACCEPTABLE letter dated 2/2/16. The proposed proprietary names, Photrexa and Photrexa Viscous, were found acceptable.

DMEPA completed a review of the draft labeling on 4/8/16. They evaluated the proposed syringe label, Tyvek® pouch labeling, foil pouch labeling, carton labeling, and insert labeling for Photrexa and Photrexa Viscous ophthalmic solutions.

11. Labeling

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 July 14, 2016 is acceptable.

12. Recommended Regulatory Action

It is recommended that the additional indication for the treatment of cornea ectasia following refractive surgery be added to 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**.**

RISK BENEFIT ASSESSMENT:
The applicant has submitted two adequate and well controlled trials for both the keratoconus (UVX-001 and UVX-002) and corneal ectasia (UVX-001 and UVX-003) indications; these trials demonstrate statistical significance between groups at Month12 favoring the CXL treatment for both indications.

The Advisory Committee voted that substantial evidence of efficacy and safety been demonstrated for the drug-device to support approval for progressive keratoconus. The Committee also voted that substantial evidence of efficacy and safety had been demonstrated to support approval for corneal ectasia following refractive surgery.

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.

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:
The applicant has agreed to conduct a clinical registry with a three year annual follow-up of patients treated for corneal ectasia following refractive surgery.

66 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/

WILEY A CHAMBERS
07/15/2016