THE OPTOMETRIST'S NEW ROLE IN KERATOCONUS MANAGEMENT

Availability of CXL changes the paradigm for care of US patients with keratoconus or corneal ectasia.

BY JOHN D. GELLES, OD

Corneal collagen crosslinking (CXL), which has been widely used outside the United States for the treatment of keratoconus and corneal ectasia, received US FDA approval last April. With this approval, the KXL UV-illumination system and the Photrexa and Photrexa Viscous riboflavin solutions (Avedro) became commercially available in this country.

In CXL, an ultraviolet light source is used to irradiate the cornea after it has been soaked in a photoenhancing riboflavin solution. The resulting photochemical reaction increases the number of molecular bonds, or crosslinks, in the corneal stroma, resulting in a stiffened and biomechanically strengthened cornea. The goal of this treatment is to halt or diminish the progressive thinning and steepening of the cornea that occurs in keratoconus and in patients with corneal ectasia after refractive surgery. Keratoconus affects approximately one in every 2,000 Americans and is the leading indication for penetrating keratoplasty (PK) worldwide.[1,2]

In the multicenter US clinical trial carried out in part at our institution, CXL with the Avedro system was shown to decrease progression of keratoconus and corneal ectasia.[3] Practitioners in the United States now have an effective intervention to offer patients with progressive keratoconus or ectasia. In the Netherlands, the introduction of CXL resulted in a dramatic reduction in PK procedures (Figure 1).[4] There is also evidence that patients experience reduced anxiety and subjectively better vision- and health-related quality of life after CXL.[5,6]

For optometrists, the incorporation of CXL into practice presents both challenges and opportunities. On one hand, CXL is an ideal opportunity for collaborative care with ophthalmologists. Optometrists can increase the frequency of monitoring exams for keratoconic and post-LASIK patients, and they can provide and be reimbursed for ongoing medical care. Additionally, optometrists will be able to successfully keep more keratoconic patients wearing contact lenses, and those lenses will be easier to fit and maintain once progression has been stopped and advanced disease has been avoided.

CHANGING PARADIGM

The challenge is that significant changes must be made in how optometrists manage patients with keratoconus. In the old paradigm, a patient might not be diagnosed with keratoconus until there was a combination of subjective and objective findings, such as visual complaints, refraction without a consistent endpoint, large changes in refractive values, reduced best corrected visual acuity, abnormal retinoscopy reflex, irregular mires on keratometry, and overt slit lamp

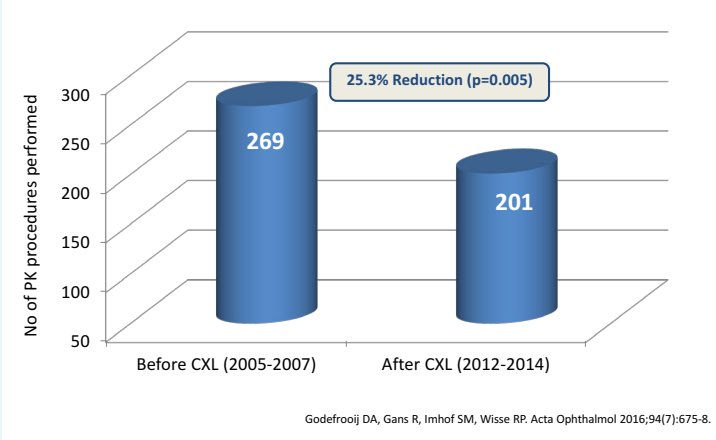

Figure 1. Comparison of penetrating keratoplasty rates during 3-year periods before and shortly after the introduction of CXL in the Netherlands.[4]

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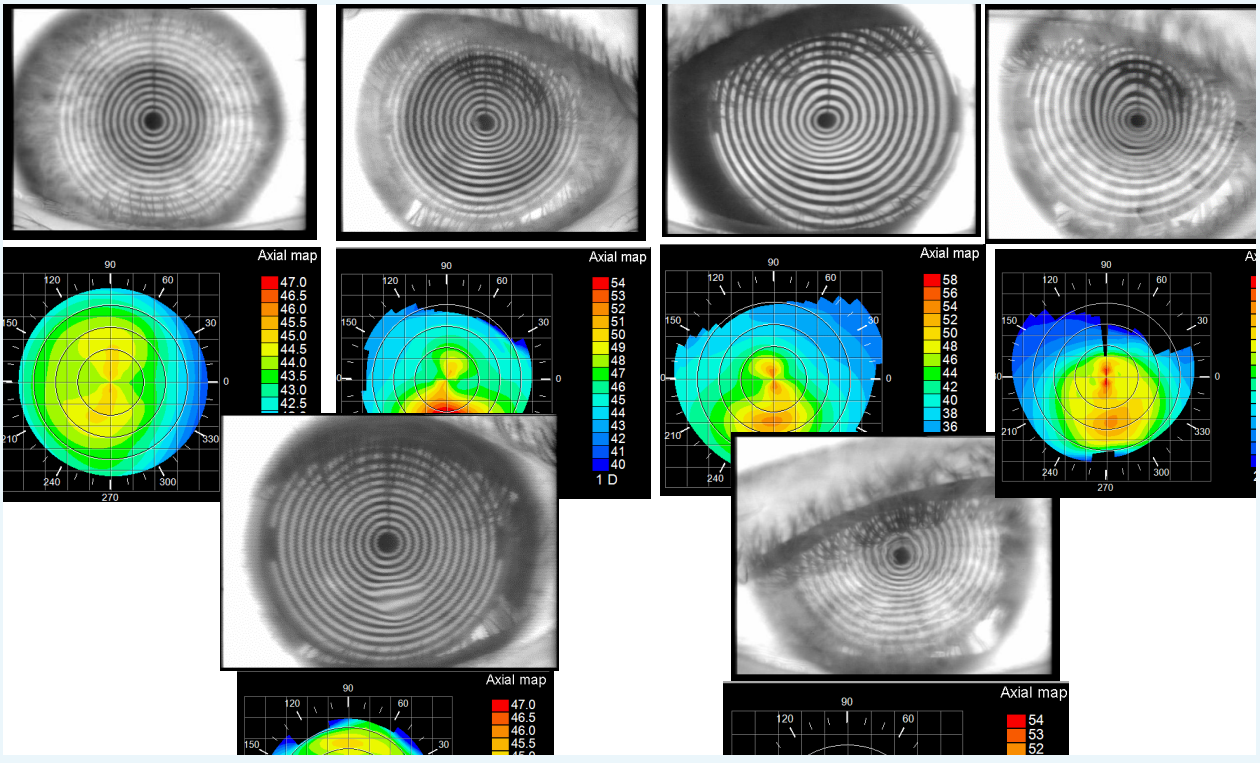

Figure 2. Comparison of topography and Placido ring mires. The metrics for diagnosis of keratoconus are K > 47.00 D, inferior-superior difference >1.40 D, 6 mm optical zone axis skew > 20° irregular astigmatism.[10] From left to right: image sets of mires with corresponding axial maps underneath. Far left image is a normal cornea with symmetric rings. Center left is an eye with keratoconus; note the irregular and asymmetric mires. Note that, in the center right image, the axial map could be mistaken for keratoconus, but on viewing the Placido ring image, it is clear the irregularity is tear film–based, whereas the far right image is true keratoconus with tear-film disruption.

TABLE. DIAGNOSTIC TECHNOLOGY TO IDENTIFY AND FOLLOW KERATOCONUS

Investment Level	Technology	Details
Minimum Investment: <$20,000	Placido ring–based corneal topography	Detect and monitor mild to advanced disease. Evaluate anterior corneal surface curvature changes. A must-have for every optometrist to monitor curvature changes.
Medium Investment: ~$65,000	All of the above, plus scanning slit or Scheimpflug-based corneal tomography	Detect and monitor early to advanced disease. Evaluate multiple key corneal metrics relevant to keratoconus and corneal ectasia.
"All in" Investment: >$100,000	All of the above, plus anterior segment OCT; corneal biomechanics; wavefront aberrometer (standalone or combined); specular microscopy	Earliest detection and most comprehensive monitoring. Evaluate all corneal metrics relevant to keratoconus, corneal ectasia, and post-CXL follow-up.

Abbreviations: CXL, corneal collagen crosslinking; OCT, optical coherence tomography

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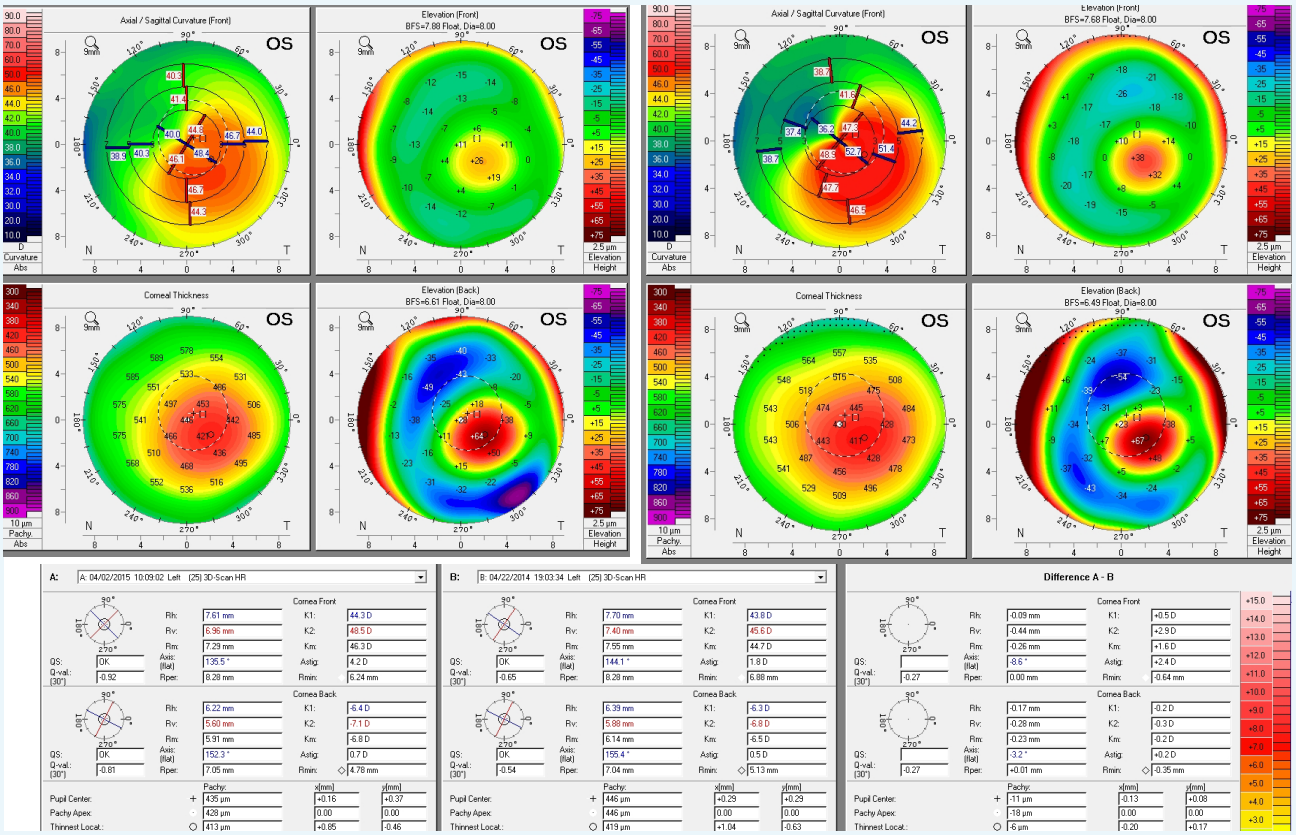

Figure 3. Case study. This patient was lost to follow-up for 1 year. The progression in this untreated eye can be seen by evaluating the mapping and noting the increases in severity that are present in all metrics. The initial map is on the left side, and a map from 1 year later is on the right side. Note the correlation of location of all metrics in keratoconus, including corneal thickness, front and back surface corneal elevation, and anterior corneal contour. The difference map on the bottom (from left to right, follow up – initial = difference) shows only the axial data, but the progression is clear to see. This tomography-based system can allow for earlier detection of keratoconus than a Placido ring–based system as it measures multiple key corneal metrics. Problems common to all topography systems include false irregularities caused by the tear film, mistaking severity of disease due to color scaling, and decentration of image capture.

signs (eg, striae, pronounced thinning, scarring, or Fleischer ring), indicating advanced disease. Follow-up included annual examinations to monitor the patient's condition, while ensuring that he or she achieved adequate vision with contact lenses and comfort without complication. Patients were typically not referred to an ophthalmologist specializing in corneal disease until they were deemed contact lens intolerant, had developed vision-impairing corneal scarring, or had progressed to such an advanced stage that PK was necessary.

With CXL, all of that changes. The earlier the patient is screened, diagnosed, and treated, the sooner one can arrest disease progression and stabilize the cornea using CXL, effectively preventing advanced disease. In recognition of this change, all of optometry and ophthalmology must now incorporate instrumentation capable of effectively screening and monitoring keratoconus. This is especially important for those working with pediatric patients, as the typical presentation of keratoconus is during adolescence.

Early diagnosis of keratoconus involves finding correlations among many corneal metrics, analogous to the correlation of metrics in diagnosing glaucoma. In keratoconus and ectatic disease, these metrics include corneal topography, corneal pachymetry, corneal epithelial thickness, posterior corneal topography, wavefront analysis, and corneal biomechanics. By and large, advanced diagnostic testing for keratoconus has not been widely incorporated into optometric practice.

In the past, even if optometrists could diagnose keratoconus at its earliest stages, they had no treatment options. However, with the advent of CXL as an effective treatment for decreasing the progression of keratoconus, it is important for all optometrists to have the equipment to diagnose and monitor the disease at its earliest stages. Thus, it is recommended that optometrists acquire, at minimum, a Placido disk–based topographer or, better yet, a corneal

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tomography-based topographer. This will allow proper screening for keratoconus. Optometric practices may want to invest in additional technologies to diagnose and monitor keratoconus and ectasia patients; cost estimates and equipment recommendations are listed in the table.

For a relatively low financial investment that can be recouped in billing for medical eye care, these instruments, which can also be used for contact lens fitting, permit evaluation of changes in several important metrics. To use such technology effectively, it is also important for optometrists to have the proper training in its interpretation. Some tips for interpretation are indicated in Figures 2 and 3.

Patients with keratoconus who are younger than 40-years-old and, thus, in the typical progressive lifecycle of the disease, should be scheduled for more frequent exams than in the past. Every 3 to 6 months is appropriate because keratoconus can rapidly progress in a short period of time at this age.

Patients with extremely advanced disease may not be good candidates for CXL, as the photochemical reaction that occurs may damage the endothelium in very thin corneas. A corneal consult is still worthwhile, however, because the hypotonic dextran-free riboflavin solution (Photrexa) can be applied to swell or thicken the cornea enough to achieve the 400-µm thickness needed for safe CXL in some cases.[7]

MANAGING THE CXL PATIENT

In the US clinical trials that led to FDA approval of the Avedro system, the corneal epithelium was removed (9.0-mm defect) before CXL was performed. Therefore, the protocol in the labeling is an epithelium-off procedure. Afterward, a bandage contact lens is placed and patients are given topical medications, typically four times daily for the first week, similar to post-PRK care. At day 5, the epithelial defect is typically healed and the bandage contact lens is removed. The antibiotic and non-steroidal anti-inflammatory drugs are discontinued, and the steroid is usually continued for another 1 to 3 weeks.

Although there is some variation, the cornea specialist will typically see patients for the 1-day and 1-week visits and then, once the epithelium is healed, send them back to the optometrist for the remainder of follow-up care.

At 1 month after CXL, visual acuity and keratometric values (Kmax) are a little worse, and it is normal to see light haze.[8] This is not the same type of haze seen after PRK; it is transient and seems to have little effect on visual acuity. After 1 month, there is progressive flattening of the Kmax; in the clinical trials for the Avedro system the flattening was an average of 1.7 D.[3] Uncorrected and best corrected visual acuity typically improve by about 1 line, and progression stops.[3]

Somewhat counterintuitively, the cornea may seem to be getting thinner; the collagen bonds tighten and the pachymetry measurements decrease; however, after about 3 months, this stabilizes along with the Kmax and visual acuity. By 1 year after CXL, pachymetry returns to baseline.[9]

Endothelial cell counts should also be checked during follow-up, as rapid changes in this metric may indicate damage to the endothelium.

Contact lenses may be fit once the epithelial integrity is restored after CXL, typically by 1 month. At that point, vaulted designs that do not rest on the corneal surface may aid in avoiding disruption of epithelial healing. It is important to make patients aware that vision may change slightly during the first few months after the procedure, and their contact lens parameters may have to be updated.

CONCLUSION

In its current iteration, CXL is not a corneal reshaping procedure. Rather, CXL is essentially a "locking-in" of the cornea so that the ectatic condition does not progress further. For fitting purposes, one can expect that the cornea may get flatter with time but likely not clinically significantly flatter; therefore, follow-up during this time is essential.

The benefits are clear: for the patient, there is an improved visual prognosis and less chance of requiring a corneal transplant; for the clinician, it will be easier to care for and provide vision correction for that patient over time. This is why early intervention is essential before there is significant further thinning and distortion.

Now that a CXL treatment is approved to slow progression, it is incumbent upon practitioners to carefully monitor and follow corneal ectatic conditions so that prompt referrals can be made for this essential procedure. ■

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PHOTREXA® VISCOUS and PHOTREXA® safely and effectively. See full prescribing information for PHOTREXA VISCOUS and PHOTREXA.

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

For use with the KXL® System
Initial U.S. Approval: 2016

RECENT MAJOR CHANGES

Indications and Usage (1.2) 7/2016

INDICATIONS AND USAGE

PHOTREXA VISCOUS and PHOTREXA are photoenhancers indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus (1.1) and corneal ectasia following refractive surgery (1.2).

DOSAGE AND ADMINISTRATION

- Debride the epithelium using standard aseptic technique using topical anesthesia (2).
- Then instill 1 drop of PHOTREXA VISCOUS topically on the eye every 2 minutes for 30 minutes (2).
- After 30 minutes, examine the eye under slit lamp for presence of a yellow flare in the anterior chamber. If flare is not detected, instill 1 drop of PHOTREXA VISCOUS every 2 minutes for an additional 2 to 3 drops and recheck for yellow flare. Repeat as necessary (2).
- Once flare is observed, perform ultrasound pachymetry. If corneal thickness is less than 400 microns, instill 2 drops of PHOTREXA every 5 to 10 seconds until the corneal thickness increases to at least 400 microns (2).
- Irradiation should not be performed unless this 400 micron threshold is met and the yellow flare is seen (2).
- Irradiate the eye for 30 minutes at 3mW/cm^2 using the KXL System as per the instructions in the KXL manual. During irradiation, continue topical instillation of PHOTREXA VISCOUS onto the eye every 2 minutes for the 30 minute irradiation period (2).
- Refer to the KXL Operator's manual for specific device instructions (2).

DOSAGE FORMS AND STRENGTHS

- PHOTREXA VISCOUS in a 3 mL glass syringe containing sterile 1.46 mg/mL riboflavin 5'-phosphate in 20% dextran ophthalmic solution (3.1)
- PHOTREXA in a 3 mL glass syringe containing sterile 1.46 mg/mL riboflavin 5'-phosphate ophthalmic solution (3.2)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

Ulcerative keratitis can occur. Monitor for resolution of epithelial defects (5)

ADVERSE REACTIONS

In progressive keratoconus patients, the most common ocular adverse reactions in any CXL-treated eye were corneal opacity (haze), punctate keratitis, corneal striae, corneal epithelium defect, eye pain, reduced visual acuity, and blurred vision (6.1). In corneal ectasia patients, 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 (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Avedro at 1-844-528-3376 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 7/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

PHOTREXA® VISCOUS and PHOTREXA® are indicated for use in corneal collagen cross-linking in combination with the KXL™ System for the treatment of

1.1 Progressive keratoconus
1.2 Corneal ectasia following refractive surgery.

2. DOSAGE AND ADMINISTRATION

Using topical anesthesia, debride the epithelium to a diameter of approximately 9 mm using standard aseptic technique. Post epithelial debridement, instill 1 drop of PHOTREXA VISCOUS topically on the eye every 2 minutes for 30 minutes.

At the end of the 30 minute soaking period, examine the eye under the slit lamp for the presence of a yellow flare in the anterior chamber. If the yellow flare is not detected, instill 1 drop of PHOTREXA VISCOUS every 2 minutes for an additional 2 to 3 drops and recheck for the presence of a yellow flare. This process can be repeated as necessary.

Once the yellow flare is observed, perform ultrasound pachymetry. If corneal thickness is less than 400 microns, instill 2 drops of PHOTREXA every 5 to 10 seconds until the corneal thickness increases to at least 400 microns. Irradiation should not be performed unless this 400 micron threshold is met and the yellow flare is seen.

Irradiate the eye for 30 continuous minutes at 3mW/cm^2 at a wavelength of 365 nm, centered over the cornea, using the KXL System as per the instructions in the KXL manual. During irradiation, continue topical instillation of PHOTREXA VISCOUS onto the eye every 2 minutes for the 30 minute irradiation period.

For topical ophthalmic use. Do not inject.

Single use PHOTREXA VISCOUS and PHOTREXA only. Discard syringe(s) after use.

PHOTREXA VISCOUS and PHOTREXA are for use with the KXL System only.

PLEASE REFER TO THE KXL OPERATOR'S MANUAL FOR SPECIFIC DEVICE INSTRUCTIONS.

3. DOSAGE FORMS AND STRENGTHS

3.1 PHOTREXA VISCOUS

PHOTREXA VISCOUS in a 3 mL glass syringe containing sterile 1.46 mg/mL riboflavin 5'-phosphate in 20% dextran ophthalmic solution for topical administration.

3.2 PHOTREXA

PHOTREXA in a 3 mL glass syringe containing sterile 1.46 mg/mL riboflavin 5'-phosphate ophthalmic solution for topical administration.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

Ulcerative keratitis can occur. Monitor for resolution of epithelial defects. [See Adverse Reactions (6)].

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling: Ulcerative keratitis [Warnings and Precautions (5)]

6.1 Clinical Trials Experience:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of the corneal collagen cross-linking procedure was

evaluated in 3 randomized, parallel-group, open-label, sham-controlled trials; patients were followed up for 12 months. Study 1 enrolled patients with progressive keratoconus or corneal ectasia following refractive surgery. Study 2 enrolled only patients with progressive keratoconus, and Study 3 enrolled only patients with corneal ectasia following refractive surgery. In each study, only one eye of each patient was designated as the study eye. Study eyes were randomized to receive one of the two study treatments (CXL or sham) at the baseline visit and were followed up at Day 1, Week 1, and Months 1, 3, 6, and 12. At Month 3 or later, sham study eyes and non-study eyes had the option of receiving CXL treatment, and were followed-up for 12 months from the time of receiving CXL treatment. Each CXL treated eye received a single course of CXL treatment only.

Safety data were obtained from: 193 randomized CXL study eyes (102 keratoconus, 91 corneal ectasia), 191 control eyes, and 319 nonrandomized CXL non-study eyes (191 keratoconus, 128 corneal ectasia). Overall, 512 eyes (293 keratoconus, 219 corneal ectasia) in 364 patients received CXL treatment.

In progressive keratoconus patients, the most common ocular adverse reactions in any CXL-treated eye were corneal opacity (haze), punctate keratitis, corneal striae, corneal epithelium defect, eye pain, reduced visual acuity, and blurred vision (Table 1).

In corneal ectasia patients, 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 patients, who did not undergo debridement or exposure to UVA light (Table 1).

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

The majority of adverse events reported resolved during the first month, while events such as corneal epithelium defect, corneal striae, punctate keratitis, photophobia, dry eye and eye pain, and decreased visual acuity took up to 6 months to resolve and corneal opacity or haze took up to 12 months to resolve. In 1-2% of patients, corneal epithelium defect, corneal edema, corneal opacity and corneal scar continued to be observed at 12 months. In 6% of corneal ectasia patients, corneal opacity continued to be observed at 12 months.

Table 1: Most Common (≥1%) Ocular Adverse Reactions in CXL-Treated Study Eye in the Pooled Randomized Safety Population – N (%)

	Progressive Keratoconus Studies		Corneal Ectasia Studies	
Preferred Term	**CXL Group (N=102)[1]**	**Control Group (N=103)[1]**	**CXL Group (N=91)[1]**	**Control Group (N=88)[1]**
Anterior chamber cell	2 (2)	0	2 (2)	1 (1)
Anterior chamber flare	4 (4)	0	5 (6)	2 (2)
Asthenopia	1 (1)	1 (1)	2 (2)	0
Blepharitis	0	0	0	1 (1)
Corneal disorder	3 (3)	1 (1)	3 (3)	0
Corneal epithelium defect	24 (24)	1 (1)	26 (28)	3 (3)
Corneal oedema	3 (3)	0	3 (3)	0
Corneal opacity[2]	65 (64)	9 (9)	65 (71)	8 (9)
Corneal striae	24 (24)	12 (12)	8 (9)	6 (7)
Corneal thinning	1 (1)	2 (2)	0	0
Diplopia	2 (2)	1 (1)	1 (1)	0
Dry eye	6 (6)	2 (2)	13 (14)	4 (5)
Eye complication associated with device	2 (2)	0	1 (1)	0
Eye discharge	2 (2)	1 (1)	0	0
Eye oedema	7 (7)	0	0	0
Eye pain	17 (17)	3 (3)	24 (26)	0
Eye pruritus	2 (2)	0	0	0
Eyelid oedema	5 (5)	0	5 (6)	1 (1)
Foreign body sensation in eyes	15 (15)	1 (1)	13 (14)	2 (2)
Glare	4 (4)	1 (1)	2 (2)	0
Halo vision	1 (1)	0	2 (2)	0
Keratitis	1 (1)	0	3 (3)	0
Lacrimation increased	5 (5)	0	9 (10)	1 (1)
Meibomian gland dysfunction	1 (1)	1 (1)	3 (3)	2 (2)
Ocular discomfort	0	0	8 (9)	0
Ocular hyperaemia	14 (14)	2 (2)	7 (8)	4 (5)
Photophobia	11 (11)	0	17 (19)	0
Punctate keratitis	25 (25)	8 (8)	18 (20)	3 (3)
Vision blurred	16 (16)	2 (2)	15 (17)	4 (5)
Visual acuity reduced	10 (10)	9 (9)	10 (11)	1 (1)
Visual impairment	3 (3)	2 (2)	4 (4)	1 (1)
Vitreous detachment	2 (2)	0	0	0

1) Results are presented as the number (%) of patients with an event from baseline to Month 3.
2) Almost all cases of corneal opacity were reported as haze.

Headache was reported in between 4 to 8% of treated patients.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Animal development and reproduction studies have not been conducted with the PHOTREXA® VISCOUS/PHOTREXA®/KXL® System. Since it is not known whether the corneal collagen cross-linking procedure can cause fetal harm or affect reproduction capacity, it should not be performed on pregnant women.

8.2. Lactation

Risk Summary

There are no data on the presence of PHOTREXA VISCOUS or PHOTREXA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for the PHOTREXA/KXL corneal collagen cross-linking procedure and any potential adverse effects on the breastfed child from the PHOTREXA/KXL corneal collagen cross-linking procedure or from the underlying maternal condition.

8.4. Pediatric Use

The safety and effectiveness of corneal collagen cross-linking has not been established in pediatric patients below the age of 14 years.

8.5. Geriatric Use

No patients enrolled in the clinical studies were 65 years of age or older.

11. DESCRIPTION

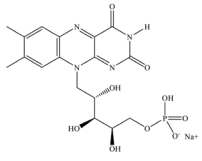
PHOTREXA VISCOUS (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146% and PHOTREXA (riboflavin 5'-phosphate ophthalmic solution) 0.146% are intended for topical ophthalmic administration as part of corneal collagen cross-linking with the KXL System.

PHOTREXA VISCOUS and PHOTREXA are supplied as:

- PHOTREXA VISCOUS in a 3 mL glass syringe containing sterile 1.46 mg/mL riboflavin 5'-phosphate in 20% dextran ophthalmic solution for topical administration.
- PHOTREXA in a 3 mL glass syringe containing sterile 1.46 mg/mL riboflavin 5'-phosphate ophthalmic solution for topical administration.

PHOTREXA VISCOUS (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146% is a yellow sterile buffered viscous solution containing 1.46 mg/mL riboflavin 5'-phosphate and 20% dextran 500. The pH of the solution is approximately 7.1 and the osmolality is 301-339 mOsm/kg. Each 1 mL of solution contains 1.53 mg of riboflavin 5'-phosphate sodium (equivalent to 1.20 mg riboflavin). Riboflavin 5'-phosphate sodium USP is a mixture of the sodium salts of riboflavin, riboflavin monophosphates, and riboflavin diphosphates. The inactive ingredients are dibasic sodium phosphate, dextran, monobasic sodium phosphate, sodium chloride, and water for injection.

PHOTREXA (riboflavin 5'-phosphate ophthalmic solution) 0.146% is a yellow sterile buffered solution containing 1.46 mg/mL riboflavin 5'-phosphate. The pH of the solution is approximately 7.1 and the osmolality is 157-177 mOsm/kg. Each 1 mL of solution contains 1.53 mg of riboflavin 5'-phosphate sodium (equivalent to 1.20 mg riboflavin). Riboflavin 5'-phosphate sodium USP is a mixture of the sodium salts of riboflavin, riboflavin monophosphates, and riboflavin diphosphates. The inactive ingredients are dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride, and water for injection.



The chemical formula for riboflavin 5'-phosphate sodium (Vitamin B2) is $C_{17}H_{20}N_4NaO_9P$ with a molecular mass of 478.33 g/mol.

Please refer to the KXL System Operator's Manual for a specific device description and instructions.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Riboflavin 5'-phosphate sodium (Vitamin B2) is the precursor of two coenzymes, flavin adenine dinucleotide and flavin mononucleotide, which catalyze oxidation/reduction reactions involved in a number of metabolic pathways.

Under the conditions used for corneal collagen cross-linking, riboflavin 5'-phosphate functions as a photoenhancer and generates singlet oxygen which is responsible for the cross-linking.

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to determine the carcinogenic potential of photoexcited riboflavin. Photoexcited

riboflavin has been shown to be genotoxic in the Ames Salmonella reverse mutation assay and in the SOS/umu test system.

The genotoxicity of riboflavin, in the absence of photoexcitation has been examined in vitro in bacterial reverse mutation assays, sister chromatid exchange assay, chromosomal aberration assays and in vivo in a mouse micronucleus study. The overall weight of evidence indicates that riboflavin, in the absence of photoexcitation, is not genotoxic.

Animal studies to determine the effects of the PHOTREXA/KXL corneal collagen cross-linking procedure on fertility were not conducted.

14. CLINICAL STUDIES

Three prospective, randomized, parallel-group, open-label, sham-controlled trials were conducted to evaluate the safety and effectiveness of riboflavin ophthalmic solution/UVA irradiation for performing corneal collagen cross-linking. These trials were sham-controlled for the first 3 months and had a total duration of 12 months for safety and efficacy evaluations. Study 1 enrolled 58 patients with progressive keratoconus and 49 patients with corneal ectasia following refractive surgery. Study 2 enrolled 147 patients with progressive keratoconus, and Study 3 enrolled 130 patients with corneal ectasia following refractive surgery. In each study, patients had one eye designated as the study eye and were randomized to receive one of two study treatments (CXL or sham) in their study eye at the baseline visit. The patients were evaluated at Day 1, Week 1, and Months 1, 3, 6, and 12. At Month 3 or later, patients had the option of receiving CXL treatment in both the sham study eyes and non-study eyes and were followed-up for 12 months from the time of receiving CXL treatment.

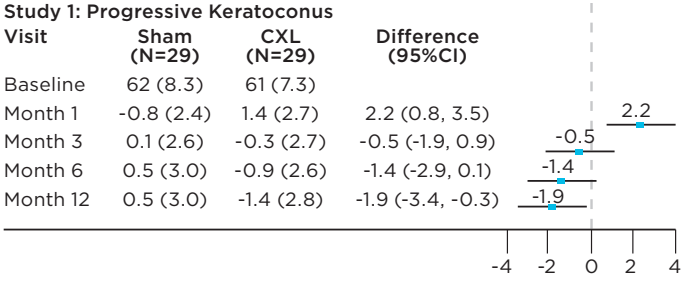
Approximately 56% and 89% of the sham study eyes in patients with progressive keratoconus received CXL treatment by Month 3 and Month 6, respectively. The average age of keratoconus patients was 33 years. The average baseline K_{max} value was 61 diopters. For corneal ectasia patients in Study 1 and Study 3, approximately 60% and 90% of the sham study eyes received CXL treatment by Month 3 and Month 6, respectively. The average age of corneal ectasia patients was 43 years and the average baseline K_{max} was 55 diopters. A majority (93%) of the corneal ectasia patients had LASIK only, 5 (3%) patients had photorefractive keratectomy (PRK) only, and 8 (4%) patients had both LASIK and PRK.

In each study, the maximum corneal curvature (K_{max}) was assessed at baseline, Months 1, 3, and 12. The CXL-treated eyes showed increasing improvement in K_{max} from Month 3 through Month 12 (Figure 1). Progressive keratoconus patients had an average K_{max} reduction of 1.4 diopters in Study 1 and 1.7 diopters in Study 2 at Month 12 in the CXL-treated eyes while the sham eyes had an average increase of 0.5 diopter in Study 1 and 0.6 diopter in Study 2 at Month 12; the difference (95% CI) between the CXL and sham groups in the mean change from baseline K_{max} were -1.9 (-3.4, -0.3) diopters in Study 1 and -2.3 (-3.5, -1.0) diopters in Study 2.

For corneal ectasia patients, at Month 12, the CXL-treated eyes had an average K_{max} reduction of 1.0 diopter in Study 1 and 0.5 diopter in Study 3 while the sham eyes had an average increase of 1.0 diopter in Study 1 and 0.5 diopter in Study 3; the treatment difference between the CXL and sham groups was: -2.0 (-3.0, -1.1) diopters in Study 1 and -1.1 (-1.9, -0.3) diopters in Study 3.

Study 1: Progressive Keratoconus

Visit	Sham (N=29)	CXL (N=29)	Difference (95%CI)
Baseline	62 (8.3)	61 (7.3)	
Month 1	-0.8 (2.4)	1.4 (2.7)	2.2 (0.8, 3.5)
Month 3	0.1 (2.6)	-0.3 (2.7)	-0.5 (-1.9, 0.9)
Month 6	0.5 (3.0)	-0.9 (2.6)	-1.4 (-2.9, 0.1)
Month 12	0.5 (3.0)	-1.4 (2.8)	-1.9 (-3.4, -0.3)



Study 2: Progressive Keratoconus

Visit	Sham (N=74)	CXL (N=73)	Difference (95%CI)
Baseline	60 (9.2)	61 (9.8)	
Month 1	0.3 (2.2)	1.2 (3.4)	0.9 (0, 1.8)
Month 3	0.2 (2.4)	-0.6 (4.4)	-0.7 (-1.9, 0.4)
Month 6	0.6 (2.8)	-1.1 (5.1)	-1.7 (-3.0, -0.3)
Month 12	0.6 (2.8)	-1.7 (4.7)	-2.3 (-3.5, -1.0)

Study 1: Corneal Ectasia

Visit	Sham (N=25)	CXL (N=24)	Difference (95%CI)
Baseline	55 (5.5)	56 (6.3)	
Month 1	0.8 (1.7)	1.1 (2.1)	0.3 (-0.8, 1.3)
Month 3	1.0 (1.7)	0.1 (1.3)	-0.9 (-1.8, -0.1)
Month 6	1.0 (1.7)	-0.6 (1.6)	-1.7 (-2.6, -0.7)
Month 12	1.0 (1.7)	-1.0 (1.7)	-2.0 (-3.0, -1.1)

Study 3: Corneal Ectasia

Visit	Sham (N=63)	CXL (N=63)	Difference (95%CI)
Baseline	55 (6.8)	55 (7.1)	
Month 1	0.0 (1.1)	1.0 (1.8)	1.0 (0.4, 1.5)
Month 3	0.6 (1.9)	-0.2 (2.4)	-0.8 (-1.6, 0.0)
Month 6	0.5 (2.3)	-0.5 (2.0)	-1.0 (-1.8, -0.3)
Month 12	0.5 (2.3)	-0.5 (2.2)	-1.1 (-1.9, -0.3)

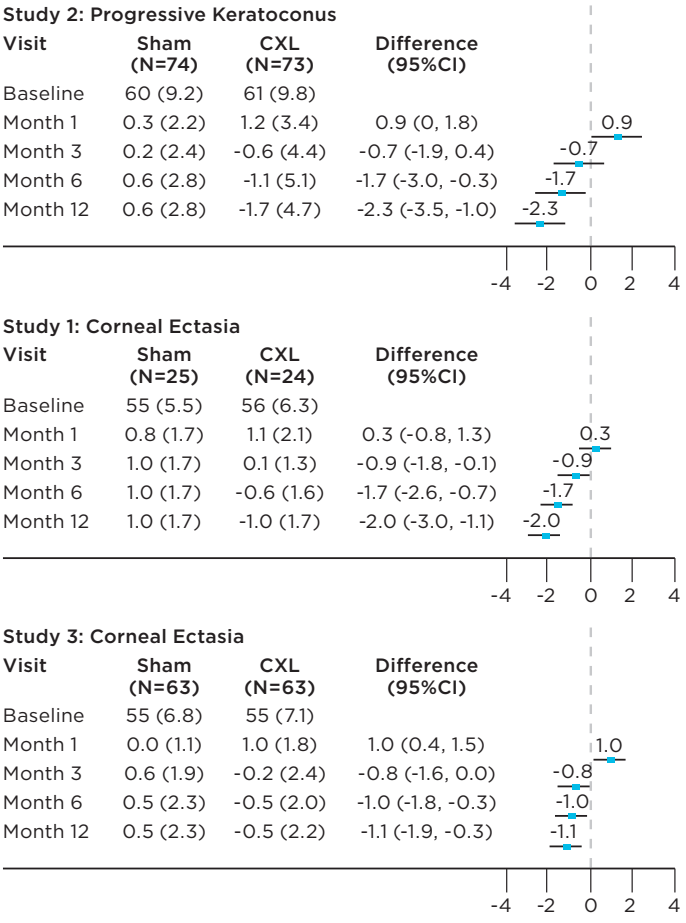


Figure 1: Mean (SD) (Diopter) Baseline K_{max} and Change from Baseline K_{max}

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. In Study 3, four patients in the CXL group had missing baseline K_{max} value and were excluded from the analysis.

16. HOW SUPPLIED/STORAGE AND HANDLING

PHOTREXA® VISCOUS and PHOTREXA® 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.

The entire bulk pack should be stored at 15°-25°C (59°-77°F) and care should be taken to minimize exposure of the syringe to light once removed from its protective packaging. Discard syringe after use.

For topical ophthalmic use.

PHOTREXA VISCOUS and PHOTREXA should be used with the KXL System only.

17. PATIENT COUNSELING INFORMATION

- Patients should be advised not to rub their eyes for the first five days after their procedure.
- Patients may be sensitive to light and have a foreign body sensation. Patients should be advised that there may be discomfort in the treated eye and that sunglasses may help with light sensitivity.
- If patients experience severe pain in the eye or any sudden decrease in their vision, they should be advised to contact their physician immediately.
- If the bandage contact lens that was placed on the patient's eye on the day of treatment falls out or becomes dislodged, the patient should be advised not to replace it and to contact their physician immediately.

PHOTREXA® VISCOUS (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%, PHOTREXA® (riboflavin 5'-phosphate ophthalmic solution) 0.146% and the KXL® System are marketed by: Avedro, 230 Third Avenue, Waltham, MA, 02451.

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