Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 3/1/20**
(See policy history boxes for previous effective dates)

Title: Corneal Collagen Cross-linking

Description/Background

Corneal collagen cross-linking (CXL) is a photochemical procedure approved by the Food and Drug Administration for the treatment of progressive keratoconus and corneal ectasia. Keratoconus is a dystrophy of the cornea characterized by progressive deformation (steepening) of the cornea while corneal ectasia is keratoconus that occurs after refractive surgery. Both lead to functional loss of vision and need for corneal transplantation.

KERATOCONUS AND ECTASIA

Keratoconus is a bilateral dystrophy characterized by progressive ectasia (paracentral steepening and stromal thinning) that impairs visual acuity. While frequently diagnosed at a young age, the progression of keratoconus is variable. Results from a longitudinal study with 7 years of follow-up showed that, over the study period, there was a decrease of 2 high- and 4 low-contrast letters in best-corrected visual acuity (BCVA).(1,2) About 1 in 5 patients showed a decrease of 10 or more letters in high-contrast visual acuity and one-third of patients showed a decrease of 10 or more letters in low-contrast visual acuity. Over 8 years of follow-up, there was a mean increase of 1.44 diopters (D) in First Definite Apical Clearance Lens (a rigid contact lens to measure corneal curvature) and 1.6 D in flatter keratometric reading.

Ectasia (also known as keratectasia, iatrogenic keratoconus, or secondary keratoconus) is a serious long-term complication of laser in situ keratomileusis (LASIK) surgery and photorefractive keratectomy. It is similar to keratoconus, but occurs postoperatively and primarily affects older populations. It may result from unrecognized preoperative keratoconus or, less frequently, from the surgery itself. Similar to keratoconus, it is characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of visual acuity.

Treatment

The initial treatment for keratoconus often consists of hard contact lenses. A variety of keratorefractive procedures have also been attempted, broadly divided into subtractive and additive techniques. Subtractive techniques include photorefractive keratectomy or laser in situ keratomileusis (LASIK), although generally, results of these techniques have been poor. Implantation of intrastromal corneal ring segments is an additive technique in which the implants are intended to reinforce the cornea, prevent further deterioration, and potentially obviate the need for penetrating keratoplasty. Penetrating keratoplasty (ie, corneal grafting) is the last line of treatment. About 20% of patients with keratoconus will require corneal transplantation. All of these treatments attempt to improve the refractive errors, but are not disease-modifying.

Treatment options for ectasia include intraocular pressure-lowering drugs, and intracorneal ring segments. Frequently, a penetrating keratoplasty is required.

None of the currently available treatment options for keratoconus and corneal ectasia halt the progression of disease and corneal transplantation is the only option available when functional vision can no longer be achieved.

Corneal collagen cross-linking (CXL) has the potential to slow the progression of disease. It is performed with the photosensitizer riboflavin (vitamin B_2) and ultraviolet A (UVA) irradiation. There are 2 protocols for CXL.

1. Epithelium-off CXL (also known as “epi-off”): In this method, about 8 mm of the central corneal epithelium is removed under topical anesthesia to allow better diffusion of the photosensitizer riboflavin into the stroma. Following de-epithelialization, a solution with riboflavin is applied to the cornea (every 1-3 minutes for 30 minutes) until the stroma is completely penetrated. The cornea is then irradiated for 30 minutes with ultraviolet A 370 nm, a maximal wavelength for absorption by riboflavin, while the riboflavin continues to be applied. The interaction of riboflavin and UVA causes the formation of reactive oxygen species, leading to additional covalent bonds (cross-linking) between collagen molecules, resulting in stiffening of the cornea. Theoretically, by using a homogeneous light source and absorption by riboflavin, the structures beyond a 400-micron thick stroma (endothelium, anterior chamber, iris, lens, retina) are not exposed to an ultraviolet dose that is above the cytotoxic threshold.
2. Epithelium-on CXL (also known as “epi-on” or transepithelial): In this method, the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed.

Currently, the only CXL treatment approved by the Food and Drug Administration (FDA) is the epithelium-off method. There are no FDA-approved CXL treatments using the epithelium-on method. CXL is being evaluated primarily for corneal stabilization in patients with progressive corneal thinning, such as keratoconus and corneal ectasia following refractive surgery. CXL may also have anti-edematous and antimicrobial properties.

Regulatory Status:

In 2016, riboflavin 5'-phosphate in 20% dextran ophthalmic solution (Photrexa Viscous®; Avedro) and riboflavin 5'-phosphate ophthalmic solution (Photrexa®; Avedro) were approved by the U.S. Food and Drug Administration for use with KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia after refractive surgery.(3)

Medical Policy Statement

The application of riboflavin with ultraviolet light for the treatment of keratoconus, also called corneal cross-linking, is considered established for patients meeting specific selection criteria.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:
Corneal collagen cross-linking using riboflavin and ultraviolet A may be considered medically necessary when one of the following conditions have been met:

- Keratoconus, when the diagnosis has been established and progression of the disease is considered likely
- Corneal ectasia after refractive surgery

Exclusions:
Corneal collagen cross-linking using riboflavin and ultraviolet A is considered experimental/investigational for all other indications.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

0402T*

Other codes (investigational, not medically necessary, etc.):

N/A

* Includes riboflavin eye drops eg. Photrexa (28)

Rationale

CORNEAL COLLAGEN CROSS-LINKING FOR KERATOCONUS AND ECTASIA
Per American Academy of Ophthalmology, treatment of progressive keratoconus is a stepladder with the least invasive measure at the starting point. Indications to maneuver care, through the less invasive steps, include patients inability to achieve adequate visual function, reasonable comfort or a stable fit.(29)

Glasses have traditionally been the first step to correct vision, moving onto contact lenses as the disease progresses. Intrastromal corneal ring segments (ICRS) may help improve contact lens tolerance and vision by reducing contour irregularities. When cataract surgery is indicated, intraocular lenses can correct myopia and regular corneal astigmatism in certain situations. The indications for considering a keratoplasty include the patients inability to achieve adequate visual function, reasonable comfort, or a stable fit with less invasive therapies.

According to the new American Academy of Ophthalmology, the primary purpose of crosslinking is to halt the progression of ectasia by improving the structural integrity of the cornea and can be considered in the early stages of the disease.(29)

Pivotal Trials
The 3 open-label RCTs are summarized in Table 1. The primary end point was a 1-diopter (D) reduction in the maximum corneal curvature (Kmax) at month 3. Because corneal stromal remodeling associated with healing response after CXL requires 6 to 12 months to stabilize, the time point for primary end point was changed from 3 to 12 months. This end point was better suited for evaluating the long-term clinical benefits of the CXL treatment. In all 3 trials, only 1 eye per patient was designated as the experimental eye. Patients with corneal ectasia diagnosed after laser in situ keratomileusis (LASIK) or photorefractive keratectomy or those with progressive keratoconus were included in these trials. Progressive keratoconus was defined as 1 or more of the following over a period of 24 months or less before randomization:

- An increase of 1 D in the steepest keratometry value
- An increase of 1 D in regular astigmatism evaluated by subjective manifest refraction
- A myopic shift (decrease in the spherical equivalent) of 0.50 D on subjective manifest refraction
- A decrease ≥0.1 mm in the back optical zone radius in rigid contact lens wearers where other information was not available.

Sham-control eyes were treated with a topical anesthetic and riboflavin solution (1 drop every 2 minutes for 30 minutes) but did not undergo epithelial débridement or have the ultraviolet A (UVA) light source turned on. For sham subjects who received CXL treatment at month 3 or month 6, the last Kmax measurement recorded prior to CXL treatment was carried forward in the analysis for later time points. This is a conservative method of analysis in this situation, because it reduces the expected worsening over time in untreated patients. Almost all patients in the sham group received CXL treatment at month 3 or 6 and therefore the analysis compared the Kmax at month 12 in the CXL group to the Kmax at month 3 or 6 in the sham group. In each study, Kmax was assessed at baseline and at months 1, 3, and 12.

Table 1. Summary of Pivotal Trial Characteristics and Results

Study	Study	Design	Dates	Patients (N or n)	Difference in Mean Change in Kmax From Baseline to 12 Months (95% CI)[b]
Unpublished	UVX-001	RCT	2008-2010	• Keratoconus (58) • Ectasia (49)	• -1.9 D (-3.4 to -0.3) • -2.0 D (-3.0 to -1.1)
Hersh et al (2011)[6,a]	UVX-002	RCT	2008-2010	Keratoconus only (147)	-2.3 D (-3.5 to -1.0)
Hersh et al (2011)[6,a,b]	UVX-003	RCT	2008-2011	Ectasia only (130)	-1.1 D (-1.9 to -0.3)

CI: confidence interval; D: diopter; Kmax: maximum corneal curvature; RCT: randomized controlled trial.
[a] Hershet al (2011)[6] reported early trial results that included data from 49 of 147 patients in the UVX-002 trial and 22 of 130 patients in the UVX-003 trial. These results are not discussed.
[b]In UVX-003, 4 patients in the collagen cross-linking group had missing baseline Kmax values and were excluded from the analysis.

Maximum Corneal Curvature (Kmax)

The CXL-treated eyes showed increasing improvement in Kmax from months 3 through 12 (data not shown). Difference of the change in Kmax from baseline to month 12 between CXL-treated eyes and sham-treated eyes is summarized in Table 1 and was statistically significant from 6 month onward in favor of CXL treatment.

Best Spectacle-Corrected Visual Acuity

The visual acuity outcomes as assessed by mean improvement in best spectacle-corrected visual acuity (BSCVA) and responder analysis (gain of ≥15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] is considered clinically meaningful) are summarized in Tables 2 and 3, respectively. Statistical procedures to control for type I error for multiple comparisons were not described in either the sponsor (7) or in FDA documents.(8,9) Therefore, these results should not be used for statistical inference. The results summarized in Tables 2 and 3 are based on last observation carried forward (LOCF) analysis. In the pooled analysis of the observed data, the mean change in sham-control patients for progressive keratoconus at 6 months was +1.1 letter (n=38) compared to +5.8 (n=96) for CXL-treated patients, yielding a difference of 4.7 letters in favor of CXL treatment. Respective numbers for patients with ectasia were -0.4 letters (n=88) versus +4 letters (n=91), yielding a difference of 4.4 letters in favor of CXL treatment. Notably, FDA-approved labels for Photrexa and Photrexa Viscous do not include any visual acuity outcomes.(3)

Table 2. Summary of BSCVA Outcomes in the Pivotal Trials

Study	Patients (n or N)	Mean Change in BSCVA From Baseline to 12 Months		Difference[a]
		CXL-Treated Eyes	*Sham-Controlled Eyes*	
UVX-001	•Keratoconus (58)	• + 7.2	• +3.4	• +3.8 letters
	•Ectasia (49)	• +5.0	• -0.9	• +5.9 letters
UVX-002	Keratoconus only (147)	+5.0	+1.4	+3.6 letters
UVX-003	Ectasia only (130)	+5.0	-0.1	+5.1 letters
Pooled	•Keratoconus (205)	• +5.6	• +2.0	• +3.6 letters
	•Ectasia (179)	• +5.0	• -0.3	• +5.3 letters

Adapted from Avedro (2015).[7]
BSCVA: best spectacle-corrected visual acuity; CXL: corneal collagen cross-linking.
[a] Results should be considered exploratory.

Table 3. Summary of ETDRS Chart Outcomes in the Pivotal Trials

Study	Patients (n or N)	Difference From Baseline to 12 Months in Percent Patients Who Gained ≥15 Letters on ETDRS		Difference[a]
		CXL-Treated Eyes	*Sham-Controlled Eyes*	
UVX-001	• Keratoconus (58) • Ectasia (49)	• +24.1% • +21.7%	• +21.4% • +4.2%	• +2.7% • +17.5%
UVX-002	Keratoconus only (147)	+17.4%	+2.8%	+14.6%
UVX-003	Ectasia only (130)	+9.2%	+4.8%	+4.4%
Pooled	• Keratoconus (58) • Ectasia (49)	• 19.4% • 12.5%	• 8.1% • 4.7%	• +11.3% • +7.8%

Adapted from Avedro (2015).[7]
CXL: corneal collagen cross-linking; ETDRS: Early Treatment Diabetic Retinopathy Study.
[a] Results should be considered exploratory.

Other Randomized Controlled Trials

Keratoconus

Hersh et al (2017) analyzed 205 patients who had keratoconus treated with CXL (n=102) or a sham procedure (n=103) in a phase 3, prospective, randomized, controlled trial.(10) At 1 year, those in the treatment group had a significant decrease in Kmax score (1.6) compared with baseline, while the control group saw an increase in Kmax (1.0); the between-group difference in Kmax change was 2.6 D (p<0.001). Mean corrected distance visual acuity (CDVA) improved significantly more in the treatment group (5.7 logMAR) than in the control group (2.2 log MAR; between-group difference, 3.5 logMAR; p<0.01). A similar finding, though statistically insignificant, was observed for mean uncorrected distance visual acuity (UDVA), with the treatment group improving by 4.4 logMAR, compared with the control group (2.6 logMAR; between-group difference, 1.8 logMAR). Endothelial cell count did not change significantly from baseline to 1 year in either group. The trial was limited in that patients in the control group were allowed to switch to CXL treatment after 3 months; thus, their data were imputed based on the LOCF method. Also, in the control group, patients did not undergo removal of their epithelium.

Renesto et al (2010) reported on 2-year results of a randomized trial that compared CXL to 1 month of riboflavin eye drops in 39 eyes of 31 patients with keratoconus.(11) After 3 months, all patients received intrastromal corneal ring segments. Patients were evaluated at 1 and 3 months after treatment with CXL or riboflavin, and then at 1, 3, 6, 12, and 24 months after ICRS insertion. There was no significant difference between the 2 groups for UCVA, BCVA, or in 3 topographic parameters (flattest-K, steepest K, and average keratometry) throughout the 24-month follow-up.

Corneal Ectasia

Hersh et al (2017) compared topographical with visual outcomes of 179 patients treated for corneal ectasia following LASIK or photorefractive keratectomy surgery.(12) The prospective, multicenter controlled trial randomized 91 patients to treatment with standard CXL and 88 patients to a sham procedure which administered riboflavin alone and did not require the removal of the epithelium. The primary end point was 1-year change in Kmax, which was a mean 0.7-D decrease in the CXL group and an 0.6-D increase in the control group (between-group difference, 1.3 D; p<0.001). A significantly greater improvement in CDVA was observed for the CXL group (5.0 logMAR gained) than for the control group (0.3 logMAR lost; p<0.001), as was the case with UDVA, for which the between-group difference was 4.6 letters (p<0.001).

There was no significant difference between treatment and control groups for either MRSE myopia or for endothelial cell density, and fewer than 5% of eyes had adverse events. Over half of patients (68%) reported corneal stromal haze or demarcation line. The trial was limited by the LOCF analysis required for the control patients who elected to receive treatment after 3 months; also, because only 4 patients received photorefractive keratectomy surgery, comparison between types of surgery and effects of post-surgery CXL were precluded.

Wittig-Silva et al (2008) reported the first randomized controlled trial (RCT) of corneal CXL.(13) Three-year results were published in 2014.(14) Recruitment for the trial was completed in 2009 with 50 eyes randomized to CXL and 50 randomized to untreated control. To be eligible for enrollment, clear evidence of progression of the ectasia over the preceding 6 to 12 months was required. Progression was confirmed if at least one of the following criteria were met: an increase of at least 1 D in the steepest simulated keratometry reading (K-max); an increase in astigmatism determined by manifest subjective refraction of at least 1 D; an increase of 0.50 D in MRSE; or a 0.1 mm or more decrease in back optic zone radius of the best fitting contact lens. At the time of analysis for the 2008 report, 20 eyes had reached 1-year follow-up. The 3-year results included 46 CXL and 48 control eyes. Last observation carried forward was used for 26 eyes, including 17 eyes from the control group with progressive disease that underwent compassionate use CXL or corneal transplantation. In the CXL group there was a flattening of Kmax by -1.03 D, compared with an increase in Kmax of 1.75 in the control group. One eye in the CXL group progressed by more than 2 D, compared with 19 eyes in the control group. Uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) improved in the CXL-treated eyes at 1, 2, and 3 years.

Systematic Reviews

Keratoconus

A Cochrane review (2015) evaluated the use of corneal CXL for treatment of keratoconus.(15) The literature search was conducted in August 2014 and did not include all of the phase 3 trials that were submitted to the FDA (described previously). Reviewers included 3 small RCTs conducted in Australia, the United Kingdom, and the United States, which enrolled a total of 225 eyes and analyzed 219 eyes. All 3 trials were at high risk for performance bias (lack of masking), detection bias (only 1 trial attempted to mask outcome assessment), and attrition bias (incomplete follow-up). Reviewers did not conduct a meta-analysis due to differences in measuring and reporting outcomes. The overall quality of the evidence was judged to be very low, primarily due to downgrading the evidence due to risk of bias in the included studies, imprecision, indirectness, and publication bias.

Meri et al (2016) reported on the results of a systematic review and meta-analysis of ocular functional and structural outcomes in patients with keratoconus who underwent CXL treatment.(16) Reviewers reported a modest but statistically nonsignificant improvement in visual acuity of 1 to 2 Snellen lines at 3 months or more after undergoing CXL. Reviewers concluded that, although CXL appeared to be effective at halting the deterioration of keratoconus, it was only slightly effective at improving visual acuity.

McAnena et al (2017) reported results of a systematic review and a meta-analysis assessing the efficacy of CXL treatment for keratoconus in pediatric patients.(17) A total of 13 articles, published between May 2011 and December 2014, examining 490 eyes of 401 patients (mean age, 15.25 years), were included in the meta-analysis. Bias assessment of individual studies

was not included. Reviewers reported a significant improvement in BCVA at 6 months (standardized mean difference [SMD], -0.66; 95% confidence interval [CI], -1.22 to -0.11; p=0.02), which was maintained at 1 year (SMD = -0.69; 95% CI, -1.15 to -0.22; p<0.01). Two-year data were available for 3 studies (n=131 eyes) and the improvement in BCVA remained significant (SMD= -1.03; 95% CI, -2 to -0.06; p=0.04).

Uncontrolled Studies

Keratoconus

Longer term follow-up is being reported from Europe, where corneal CXL has been performed for a greater number of years. Indications for treatment typically include progression of steepening (increase in K-max by at least 1 D in 1 year), deteriorating visual acuity, or the need to be fitted for new contact lenses more than once in 2 years. The largest and longest series to date are described next.

Toprak et al (2017) retrospectively analyzed 29 eyes from pediatric patients (age range, 10-17 years) whose progressive keratoconus was treated with unilateral CXL treatment.(18) From baseline to 2-year follow-up, there was a significant decrease in mean CDVA (0.34 logMAR to 0.13 logMAR; p<0.001). Maximum keratometry (Kmax) measures decreased from baseline 54.65 to 53.25 at 2 years (p=0.034), while anterior chamber parameters, corneal thickness, and corneal volume were not significantly affected by CXL after 2 years (p>0.05). Several parameters of the Scheimpflug imaging system were improved following CXL treatment: index of surface variance (ISV) decreased from 69.75 at baseline to 62.95 at 2 years (p=0.004); keratoconus index (KI) decreased from 1.16 (p=0.001); center keratoconus index (CKI) decreased from 1.05 to 1.04 (p=0.004); and index of height decentration (IHD) decreased from 0.056 to 0.042 (p=0.001). Radius of minimum curvature (Rmin) increased significantly from baseline to 2 years (6.21 to 6.36; p=0.007), although 2 other indices (indices of height and vertical asymmetry) did not change significantly. The authors noted that follow-up beyond 2 years is required to make long-term assessments of CXL as treatment for keratoconus, but concluded that their results seemed favorable for postoperative outcomes.

Badawi et al (2017) published a prospective nonrandomized observational study of accelerated CXL to treat pediatric patients with keratoconus.(19) Of the 25 patients (33 eyes) enrolled, 80% were male, and most patients (n=17) received unilateral CXL, administered with Vibex Rapid solution and Vega CBM X-Linker. The group's mean unaided and aided visual acuity were significantly improved at all time points (3, 6, and 12 months): at 12-month follow-up, the mean unaided visual acuity score was 0.34, which was a significant decrease compared with preoperative mean score (0.54; p<0.001). For aided visual acuity, there was a similar decrease from preoperative (0.36) to 12-month (0.17 time points (p<0.001). Mean corneal astigmatism values also decreased significantly (preoperative 2.4 D decreased to 2.01 D at 12 months; p<0.001). The mean Kmax showed an average flattening of 1.2 D in 1 year (49.12 D decreasing to 47.9 D; p<0.001); the authors reported significant improvements in other measures such as central pachymetry, maximum anterior elevation, average progression indices, and Q values. A limitation of the study was the slight increase observed in posterior surface elevation, which, contrary to other study measures, showed no significant positive effect 12 months after accelerated CXL (p=0.9). Advising further study of the procedure, the authors noted that the unusual result might be accounted for by the choice of Pentacam as a corneal analysis tool, because there might have been corneal artifacts present during evaluation.

Knutsson et al (2018) published a prospective cohort study of 43 patients (52 eyes) between the ages of 12 and 17 who underwent CXL as treatment for keratoconus in 1 or both eyes.(20) Two-year outcomes were reported for all patients, although longer-term (up to 7 years) follow-up was available for 21 eyes. At 2 years, overall mean Kmax decreased from 59.30 ± 7.08 to 57.07 ± 6.46 ($p<0.001$), and overall mean UCVA and BSCVA decreased, although not significantly. Additional analyses were conducted of patients whose eyes had Kmax values of 60 D or greater (n=25), compared with those whose keratometry was less severe (<60 D). As with the overall findings, mean Kmax for both cohorts was significantly decreased for both cohorts, while neither UCVA nor BSCVA measures changed significantly at 1 or 2 years. In patients with advanced keratoconus, mean Kmax decreased from 64.94 (95% CI, 62.94 to 66.94) to 62.25 (95% CI, 60.55 to 63.95) at 2 years ($p<0.001$); for the less-advanced cohort, mean Kmax decreased from 53.88 (95% CI, 52.48 to 55.28) at baseline to 52.08 (95% CI, 50.68 to 53.48) at 2 years ($p<0.001$). While most findings were favorable for the efficacy of CXL in treating even severe keratometry, the authors noted that the study was limited by the use of 2 pachymetric measurement techniques (optical coherence tomography and ultrasound) rather than a single technique across the study. Further, the lack of full long-term data for all patients limited the study to reporting only 2-year outcomes.

Padmanabhan et al (2016) retrospectively analyzed 377 eyes of 336 patients (mean age, 15 years) who underwent CXL for progressive keratoconus.(5) There was significant improvement in mean BSCVA from 0.33 to 0.27 logMAR ($p<0.05$). The authors found that the benefits of CXL in stabilizing keratoconus were maintained for more than 2 years in most pediatric eyes. Padmanabhan et al (2017) also published follow-up results from the retrospective study previously mentioned of 377 eyes in 336 pediatric patients.(21) Of 59 eyes for which investigators had longer term follow-up data (4 to 6.7 years), 30.9% showed worsening CDVA, and 24% showed corneal steepening of greater than 1 D (Kmax). These results showed the majority of patients still experienced improvements or stabilization of keratoconus-related outcomes after CXL, but suggested that, long term, there may be less efficacy.

Raiskup-Wolf et al (2008) reported outcomes of 241 eyes (130 patients) treated with CXL, with a minimum of 6 months' follow-up.(22) Follow-up examinations were performed at 1, 6, and 12 months, and then annually. Mean follow-up was 26 months with a range of 12 months (n=142) to 6 years (n=5). In the first year (n=142), steepening (K-max) improved or remained stable in 86% of eyes, and BCVA improved by at least 1 line in 53% of the eyes. Three years after treatment (n=33), K-max improved by a mean of 2.57 D in 67% of eyes while BCVA improved by at least 1 line in 58% of eyes. In 2015, the same group published 10-year follow-up of CXL treatment in 34 eyes (24 patients) with progressive keratoconus.(23) Mean patient age at the time of treatment was 28 years (range, 14-42). Corneal steepening improved slightly between baseline and 10-year follow-up ($p<0.001$), while corrected distance visual acuity improved by 0.14 logMAR ($p=0.002$). Two eyes had repeat CXL, one at 5 years and one at 10 years, without adverse sequelae. One of the 34 eyes treated developed a permanent corneal scar. These studies are limited by the retrospective nature and the small number of cases with extended follow-up.

A publication from the Siena Eye Cross Study (2010) reported on a 52 month mean follow-up (range, 48-60 months) for 44 keratoconic eyes treated with CXL.(24) Follow-up evaluations were performed at 1, 2, 3, 6, 12, 24, 36, 48, and 60 months after CXL. Topographic analysis showed a mean K reading reduction of -1.96 D after 1 year, -2.12 D after 2 years, -2.24 D after

3 years, and -2.26 D after 4 years of follow-up. By comparison, in fellow eyes untreated for the first 24 months, the mean K value increased by 1.2 D at 1 year and 2.2 D at 2 years. In treated eyes, UCVA improved by a mean of 2.41 lines after 12 months, 2.75 lines after 24 months, 2.80 lines after 36 months, and 2.85 lines after 48 months. There was no significant decrease in endothelial cell density, central corneal thickness, or intraocular pressure over follow-up. Temporary adverse effects included stromal edema in the first 30 days (70% of patients) and temporary haze (9.8% of patients). No persistent adverse effects were observed.

A publication from the Siena CXL Pediatrics trial (2012) reported 12- to 36-month follow-up after CXL in 152 patients aged 18 years or younger with keratoconus progression.(25) Visual acuity increased by an average of 0.15 Snellen lines (a clinically relevant change is generally considered to be 2 Snellen lines).

The French National Reference Center for Keratoconus published their findings in 2011.(26) Of 142 eyes enrolled in the study, 6-month follow-up was available for 104 (73%), and 12-month follow-up was available for 64 (45%). At 12 months after treatment, the BCVA had stabilized in 48% of eyes, improved in 40%, and decreased in 12%. Keratoconus progression had stopped in 69%, and K-max had decreased by more than 2 D in 21% of eyes. There was a 7% complication rate in the total sample, with 5 eyes (3.5% of 142 or 7.8% of 64) losing 2 or more Snellen lines of visual acuity. This retrospective study had a low proportion of patients available at 12-month follow-up.

Adverse Events

The safety analysis conducted by FDA included 512 eyes (293 keratoconus, 219 corneal ectasia) in 364 patients who received CXL treatment.(3,8) As described earlier, the procedure involves removing the corneal epithelium to enhance the riboflavin solution's penetration. As a result, patients may develop a range of ocular adverse reactions, including corneal opacity (haze), corneal epithelial defects, punctate keratitis, corneal striae, eye pain, reduced visual acuity, blurred vision, dry eye, and photophobia among others. Most adverse reactions resolved in the first month, while others took up to 12 months to resolve. However, in 1% to 6% of patients, these adverse reactions could continue beyond 12 months.

SUMMARY OF EVIDENCE

For individuals who have progressive keratoconus who receive collagen cross-linking (CXL) using riboflavin and ultraviolet A, the evidence includes multiple randomized controlled trials (RCTs), systematic reviews, and nonrandomized studies. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. In both pivotal RCTs, the primary end point (an intermediate outcome) of reducing maximum corneal curvature (Kmax) by 1 diopter (D) was achieved at month 3 and maintained at months 6 and 12 in CXL-treated patients, compared to sham controls. In the 2 RCTs, the difference in mean change in Kmax from baseline to 12 months was 1.9 and 2.3 D, respectively, favoring the CXL-treated patients. Long-term follow-up for visual acuity outcomes are needed. The adverse events associated with CXL include corneal opacity (haze), corneal epithelial defects, and other ocular findings. Most adverse events resolved in the first month but, in a few (1%-6%) patients, continued for 6 to 12 months. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have corneal ectasia after refractive surgery who receive CXL using riboflavin and ultraviolet A, the evidence includes multiple RCTs, systematic reviews, and

nonrandomized studies. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. In both pivotal RCTs, the primary end point (an intermediate outcome) of reducing Kmax by 1 D was achieved at month 3 and maintained at months 6 and 12 in the CXL-treated patients compared to sham controls. In the 2 RCTs, the difference in mean change in Kmax from baseline to 12 months was 2.0 and 1.1 D, respectively, favoring CXL-treated patients. Long-term follow-up for visual acuity outcomes are needed. The adverse events associated with CXL include corneal opacity (haze), corneal epithelial defects, and other ocular findings. Most adverse events resolved in the first month, but, in a few (1%-6%) patients, continued for 6 to 12 months. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental information

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

In response to requests, Blue Cross Blue Shield Association received input from 1 physician specialty society and 1 academic medical center (2 reviewers) while this policy was under review in 2012. The input from all reviewers was mixed, noting the limited literature and lack of FDA approval for this procedure, although there are ongoing FDA-regulated clinical trials. The reviewers also commented on the lack of alternatives to slow the progression of disease and that data indicate that the procedure is safe and effective enough to offer to patients with adequate informed consent under an investigational protocol.

PRACTICE GUIDELINES AND POSITION STATEMENTS

The American Academy of Ophthalmology (2017) issued recommendations regarding the use of CXL as follows:(30)

> “Cross-Linking (CXL) has long term data supporting its safety and stability and should be considered for patients with early Keratoconus and at risk of progression to arrest or slow progression in its earliest stage.”

The National Institute for Health and Care Excellence (2013) issued guidance on corneal collagen cross-linking (CXL) using riboflavin and ultraviolet A, updating its 2009 guidance.(27) The 2013 guidance stratified NICE recommendations for corneal CXL as follows:

> “Most of the published evidence on photochemical corneal collagen cross-linkage (CXL) using riboflavin and ultraviolet A (UVA) for keratoconus and keratectasia relates to the technique known as 'epithelium-off' CXL'. 'Epithelium-on (transepithelial) CXL' is a more recent technique and less evidence is available on its safety and efficacy. Either procedure (epithelium-off or epithelium-on CXL) can be combined with other interventions, and the evidence base for these combination procedures (known as 'CXL-plus') is also limited. Therefore, different recommendations apply to the variants of this procedure, as follows:
>
> 1.1 Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia is adequate in quality and quantity. Therefore, this procedure can be used provided that normal arrangements are in place for clinical governance, consent and audit.
> 1.2 Current evidence on the safety and efficacy of epithelium-on (transepithelial) CXL, and the combination (CXL-plus) procedures for keratoconus and keratectasia is

inadequate in quantity and quality. Therefore, these procedures should only be used with special arrangements for clinical governance, consent and audit or research".

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00560651	German Corneal Cross Linking Registry	7500	Nov 2017 (ongoing)
NCT01708538[a]	Phase III Study of Corneal Collagen Cross-linking Using Two Different Techniques	30	Oct 2020
NCT01604135	Collagen Crosslinking for Keratoconus – a Randomized controlled Clinical Trial	200	May 2019
NCT03319082[a]	A Phase IV Observational Registry to Assess the Durability of Effect of Corneal Collagen Cross-linking With Photrexa Viscous, Photrexa, and the KXL System in Patients With Corneal Ectasia Following Refractive Surgery	200	Jul 2023
Unpublished			
NCT01459679	A Multi-Center, Randomized, Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus or Corneal Ectasia After Refractive Surgery	4000	Jan 2016 (terminated)
NCT01344187[a]	A Multi-Center, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus	236	Jun 2016 (completed)
NCT01972854[a]	A Multi-Center, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus	92	Apr 2017 (terminated)
NCT01189864[a]	Collagen Crosslinking With Ultraviolet-A in Asymmetric Corneas	500	Dec 2018 (terminated)
NCT02721628	Femtosecond Laser Assisted Epi-keratoplasty Versus Collagen Cross-Linking in Progressive Keratoconus	60	Mar 2018

NCT: national clinical trial
[a] Denotes industry-sponsored or cosponsored trial

Government Regulations

National:

There is no National Coverage Determination.

Local:

There is no Local Coverage Determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are

updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Refractive Keratoplasties and Implantation of Intrastromal Corneal Ring Segments

References

1. Davis LJ, Schechtman KB, Wilson BS et al. Longitudinal changes in visual acuity in keratoconus. Invest Ophthalmol Vis Sci 2006; 47(2):489-500.
2. McMahon TT, Edrington TB, Szczotka-Flynn L et al. Longitudinal changes in corneal curvature in keratoconus. Cornea 2006; 25(3):296-305.
3. Avedro Inc. Photorexa® Viscous and Photorexa® Prescribing Label; retrieved February 23, 2018 from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203324s000lbl.pdf.
4. Chunyu T, Xiujun P, Zhengjun F, et al. Corneal collagen cross-linking in keratoconus: a systematic review and meta-analysis. Sci Rep. 2014;4:5652. PMID 25007895
5. Papaioannou L, Miligkos M, Papathanassiou M. Corneal Collagen Cross-Linking for Infectious Keratitis: A Systematic Review and Meta-Analysis. *Cornea.* Jan 2016;35(1):62-71. PMID 26509768
6. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. J Cataract Refract Surg 2011; 37(1):149-60.
7. Avedro Inc . Avedro Briefing Package for Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Device Panel of the Medical Devices Advisory Committee NDA 203324: Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and KXL System (UVA light source) Avedro, Inc. 2015; retrieved May 9, 2017 from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM435022.pdf.
8. Center for Drug Evaluation and Research: FDA. Summary Review: Application Number 203324Orig2s000; retrieved February 23, 2018 from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/203324Orig2s000SumR.pdf.
9. U.S. Food and Drug Administration. FDA Briefing Package for Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Device Panel of the Medical Devices Advisory Committee NDA 203324: Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and KXL System (UVA light source) Avedro, Inc. 2015; retrieved May 9, 2017 from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM435021.pdf.
10. Hersh PS, Stulting RD, Muller D, et al. United States multicenter clinical trial of corneal collagen crosslinking for keratoconus treatment. Ophthalmology. Sep 2017;124(9):1259-1270. PMID 28495149
11. Renesto Ada C, Barros Jde N, Campos M. Impression cytologic analysis after corneal collagen cross-linking using riboflavin and ultraviolet-A light in the treatment of keratoconus. *Cornea.* Oct 2010;29(10):1139-1144. PMID 20622670

12. Hersh PS, Stulting RD, Muller D, et al. U.S. multicenter clinical trial of corneal collagen crosslinking for treatment of corneal ectasia after refractive surgery. Ophthalmology. Oct 2017;124(10):1475-1484. PMID 28655538
13. Wittig-Silva C, Whiting M, Lamoureux E et al. A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. J Refract Surg 2008; 24(7):S720-5.
14. Wittig-Silva C, Chan E, Islam FM et al. A Randomized, Controlled Trial of Corneal Collagen Cross-Linking in Progressive Keratoconus: Three-Year Results. Ophthalmology 2014. Renesto Ada C, Barros Jde N, Campos M. Impression cytologic analysis after corneal collagen cross-linking using riboflavin and ultraviolet-A light in the treatment of keratoconus. Cornea 2010; 29(10):1139-44.
15. Sykakis E, Karim R, Evans JR, et al. Corneal collagen cross-linking for treating keratoconus. *Cochrane Database Syst Rev.* 2015;3:CD010621. PMID 25803325
16. Meiri Z, Keren S, Rosenblatt A, et al. Efficacy of corneal collagen cross-linking for the treatment of keratoconus: a systematic review and meta-analysis. Cornea. Mar 2016;35(3):417-428. PMID 26751990
17. McAnena L, Doyle F, O'Keefe M. Cross-linking in children with keratoconus: a systematic review and meta-analysis. Acta Ophthalmol. Sep 28 2016. PMID 27678078
18. Toprak I, Yaylali V, Yildirim C. Visual, topographic, and pachymetric effects of pediatric corneal collagen cross-linking. J Pediatr Ophthalmol Strabismus. Mar 1 2017;54(2):84-89. PMID 27668869
19. Badawi AE. Accelerated corneal collagen cross-linking in pediatric keratoconus: One year study. Saudi J Ophthalmol. Jan-Mar 2017;31(1):11-18. PMID 28337057
20. Knutsson KA, Paganoni G, Matuska S, et al. Corneal collagen cross-linking in paediatric patients affected by keratoconus. Br J Ophthalmol. Feb 2018;102(2):248-252. PMID 28655729
21. Padmanabhan P, Rachapalle Reddi S, Rajagopal R, et al. Corneal collagen cross-linking for keratoconus in pediatric patients-long-term results. Cornea. Dec 01 2016. PMID 27918352
22. Raiskup-Wolf F, Hoyer A, Spoerl E et al. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. J Cataract Refract Surg 2008; 34(5):796-801.
23. Raiskup F, Theuring A, Pillunat LE, et al. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. J Cataract Refract Surg. Jan 2015;41(1):41-46. PMID 25532633
24. Caporossi A, Mazzotta C, Baiocchi S et al. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. Am J Ophthalmol 2010; 149(4):585-93.
25. Caporossi A, Mazzotta C, Baiocchi S et al. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. Cornea 2012; 31(3):227-31.
26. Asri D, Touboul D, Fournie P et al. Corneal collagen crosslinking in progressive keratoconus: multicenter results from the French National Reference Center for Keratoconus. J Cataract Refract Surg 2011; 37(12):2137-43.
27. National Institute for Health and Care Excellence (NICE). Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus and keratectasia [IPG466]. 2013; retrieved May 28, 2019 from: https://www.nice.org.uk/guidance/ipg466.
28. Centers for Medicare & Medicaid Services (CMS) Healthcare Common Procedure Coding System (HCPCS). HCPCS code application summary. May 17, 2017; retrieved March 13,

2018 from: https://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/Downloads/2017-05-17-HCPCS-Application-Summary.pdf.
29. American Academy of Ophthalmology (AAO). CXL for Corneal Ectasia: Reshaping the Future of Treatment. Retrieved July 1, 2019 from: https://www.aao.org/eyenet/article/cxl-corneal-ectasia-reshaping-future-of-treatment-2.
30. American Academy of Ophthalmology (AAO). Cornea/External Disease Summary Benchmarks – 2018. AAP PPP Cornea/External Disease Panel, Hoskins Center for Quality Eye Care. Nov 2017. Retrieved July 2, 2019 from: https://www.aao.org/summary-benchmark-detail/cornea-external-disease-summary-benchmarks-2018.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through October 8, 2019, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/12	10/11/11	11/9/11	Joint policy established
5/1/13	2/19/13	3/4/13	Routine maintenance; BCBSA policy incorporated into updated policy; title changed from **"**Riboflavin Application with UVA for the Treatment of Keratoconus (Corneal Cross-Linking)" to current title
11/1/14	8/21/14	8/25/14	Routine maintenance
11/1/15	8/24/15	9/14/15	Routine maintenance
11/1/16	8/16/16	8/16/16	Routine maintenance T code replaced NOC code
11/1/17	8/31/17	8/25/17	• Routine maintenance • Changed to mixed status • Codes added 65435, 69990, 76514 • FDA approval for New Drug Application added
11/1/18	8/21/18	8/21/18	• Routine maintenance
11/1/19	9/20/19		• Routine maintenance • Discussion regarding conservative therapy prior to surgery • Conservative therapy and progression of keratoconus requirements removed from inclusions
3/1/20	12/17/19		• Routine maintenance

Next Review Date: 4th Qtr, 2020

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CORNEAL COLLAGEN CROSS-LINKING

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.