Corneal Collagen Cross-Linking

Policy Number: 9.03.28
Origination: 5/2016

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Corneal Collagen Cross-Linking when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Corneal collagen cross-linking using riboflavin and ultraviolet A may be considered medically necessary as a treatment of progressive keratoconus or corneal ectasia after refractive surgery.

When Policy Topic is not covered
Corneal collagen cross-linking using riboflavin and ultraviolet A is considered investigational for all other indications.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: With progressive keratoconus</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td></td>
<td>Corneal collagen cross-linking using riboflavin and ultraviolet A</td>
<td>Observation, Rigid or specialty contact lens, Intracorneal ring segments, Corneal transplant</td>
<td>Change in disease status, Functional outcomes, Treatment-related morbidity</td>
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<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
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Corneal collagen cross-linking (CXL) is a photochemical procedure that is approved by the Food and Drug Administration for the treatment of progressive keratoconus and corneal ectasia. Keratoconus is a naturally occurring 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.

For individuals who have progressive keratoconus who receive 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 the Kmax by 1 diopter was achieved at month 3 and maintained at months 6 and 12, compared to sham controls. The sham-controlled reduction in Kmax was 1.9 and 2.3 D with CXL treatment in patients with keratoconus respectively in the 2 RCTs. Long-term follow-up for visual acuity outcomes are needed. The adverse events associated with this procedure include corneal opacity (haze), corneal epithelial defects, and other ocular findings. Most of these adverse events resolve in the first month but, in a few (1%-6%) patients, may continue 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 the Kmax by 1 diopter was achieved at month 3 and maintained at months 6 and 12, compared to sham controls. The sham-controlled reduction in Kmax was 2.0 and 1.1 D with CXL treatment in patients with ectasia respectively in the 2 RCTs. Improvement in visual acuity outcomes were numerically greater in the patients treated with CXL compared with sham controls. Long-term follow-up for visual acuity outcomes are needed. The adverse events associated with this procedure include corneal opacity (haze), corneal epithelial defects, and other ocular findings. Most of these adverse events resolve in the first month but in a few (1%-6%) patients may continue for 6 to 12 months. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Background**

Corneal collagen cross-linking (CXL) is performed with the photosensitizer riboflavin (vitamin B2) 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 370 nm ultraviolet A, 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.

Keratoconus is a bilateral dystrophy that is 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 a 7-year 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). About 1 in 5 patient showed a decreases of 10 or more letters in high-contrast visual acuity and one-third of patients showed a decreases 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.

Initial treatment 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 (see evidence review in separate policy) 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. In contrast, corneal CXL has the potential to slow the progression of disease.

Ectasia (also known as keratectasia, iatrogenic keratoconus, or secondary keratoconus) is a serious long-term complication of LASIK surgery and photorefractive keratectomy. It is similar to keratoconus, but occurs postoperatively and primarily affects older population. 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 options 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.

**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 (FDA) for use with KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia after refractive surgery.\(^{(3)}\)

**Rationale**

This evidence review was originally created in March 2012 and has been updated regularly using the MEDLINE database. The most recent literature update was performed through January 25, 2017.

**PIVOTAL TRIALS**

The evidence base for Food and Drug Administration (FDA) approval of epi-off corneal collagen cross-linking (CXL) for the treatment of progressive keratoconus and corneal ectasia after refractive surgery consists of 3 randomized, parallel-group, open-label, sham-controlled trials that are summarized below. In addition, there are systematic reviews, 2 randomized controlled trials (RCTs), and multiple prospective controlled studies as well as uncontrolled trials reporting on longer term outcomes of the procedure.\(^{(4,5)}\) These RCTS are summarized in the next section.

The 3 RCTs summarized in Table 1. The primary end point was a 1 diopter (D) reduction in the maximum corneal curvature (abbreviated as 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 because it was better suited for evaluating the long-term clinical benefits of the CXL treatment. In all 3 trials, only 1 eye per patients was designated as 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 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 compares 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, months 1, 3, and 12.

Table 1. Summary of Pivotal Trial Characteristics and Results

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Design</th>
<th>Dates</th>
<th>Patients (N or n)</th>
<th>Mean Change in Kmax at 12 Months (95% CI)b</th>
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</thead>
<tbody>
<tr>
<td>Unpublished</td>
<td>UVX-001</td>
<td>RCT</td>
<td>2008-2010</td>
<td>Keratoconus (58) Ectasia (49)</td>
<td>-1.9 D (-3.4 to -0.3) -2.0 D (-3.0 to -1.1)</td>
</tr>
<tr>
<td>Hersh (2011)a</td>
<td>UVX-002</td>
<td>RCT</td>
<td>2008-2010</td>
<td>Keratoconus only (147)</td>
<td>-2.3 D (-3.5 to -1.0)</td>
</tr>
<tr>
<td>Hersh (2011)a,b</td>
<td>UVX-003</td>
<td>RCT</td>
<td>2008-2011</td>
<td>Ectasia only (130)</td>
<td>-1.1 D (-1.9 to -0.3)</td>
</tr>
</tbody>
</table>

CI: confidence interval; D: diopter; Kmax: maximum corneal curvature; RCT: randomized controlled trial.
a This article reported early results of the trial that included data from 49 of 147 patients in UVX-002 trial and 22 of 130 patients in UVX-003 trial. These results are not discussed.
b In UVX-003, 4 patients in the CXL group had missing baseline Kmax value and were excluded from the analysis.

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

Best Spectacle-Corrected Visual Acuity (ETDRS Letters Read)
The visual 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
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 group for progressive keratoconus at 6 months was +1.1 letter (n=38) compared to +5.8 (n=96) for CXL 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.

Table 2. Summary of Results on Visual Outcomes in the Pivotal Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>Mean Change in BSCVA from Baseline to 12 Months</th>
<th>Differencea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CXL-Treated Eyes</td>
<td>Sham-Controlled Eyes</td>
</tr>
<tr>
<td>UVX-001</td>
<td>Keratoconus (58)</td>
<td>+ 7.2</td>
<td>+3.4</td>
</tr>
<tr>
<td></td>
<td>Ectasia (49)</td>
<td>+5.0</td>
<td>-0.9</td>
</tr>
<tr>
<td>UVX-002</td>
<td>Keratoconus only (147)</td>
<td>+5.0</td>
<td>+1.4</td>
</tr>
<tr>
<td></td>
<td>Ectasia only (130)</td>
<td>+5.0</td>
<td>-0.1</td>
</tr>
<tr>
<td>Pooled</td>
<td>Keratoconus (205)</td>
<td>+5.6</td>
<td>+2.0</td>
</tr>
<tr>
<td></td>
<td>Ectasia (179)</td>
<td>+5.0</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

CXL: corneal collagen cross-linking; ETDRS: Early Treatment Diabetic Retinopathy Study.

a Results should be considered exploratory.

MISCELLANEOUS RANDOMIZED CONTROLLED TRIALS

Wittig-Silva et al reported the first RCT of corneal CXL in 2008.(11) Three-year results were published in 2014.(12) Recruitment for the trial was completed in 2009 with 50 eyes randomized to CXL treatment and 50 randomized to untreated control. To be eligible for enrollment, clear evidence of progression of ectasia over the preceding 6 to 12 months was required. Progression was confirmed if at least 1 of the following criteria were met: an increase of at least 1 D in the steepest simulated keratometry reading (Kmax); an increase in astigmatism determined by manifest subjective refraction of at least 1 D; an increase of 0.50 D in manifest refraction spherical equivalent; 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-treated and 48 control eyes. LOCF 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 BCVA improved in the CXL-treated eyes at 1, 2, and 3 years. In control eyes, UCVA was significantly reduced at 36 months (p=0.034) and there was a trend of a decrease in BCVA (p=0.10). The difference between groups in UCVA was significant (p<0.001). Follow-up is continuing through 5 years.

In 2012, Renesto et al reported 2-year results of a randomized trial that compared CXL versus 1 month of riboflavin eye drops in 39 eyes of 31 patients with
keratoconus. After 3 months, all patients received intrastromal corneal ring segments (ICRS; see evidence review in a separate policy). 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.

**SYSTEMATIC REVIEWS**
A Cochrane review on the use of corneal CXL for the treatment of keratoconus was published in 2015. The literature search for this systematic review was conducted in August 2014 and does not include all of the phase 3 trials that were submitted to FDA (described previously). This review included 3 small RCTs conducted in Australia, the United Kingdom, and the United States that enrolled a total of 225 eyes and analyzed 219 eyes. All 3 studies 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). The authors 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.

In 2016, Meri et al reported results of a systematic review and meta-analysis of ocular functional and structural outcomes in patients with keratoconus who underwent CXL treatment. 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 appears to be effective for halting the deterioration of keratoconus it was only slightly effective at improving visual function.

McAnena et al (2016) reported results of a systematic review and a meta-analysis assessing the efficacy of CXL treatment for keratoconus in pediatric patients. 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 was available in 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**
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 Kmax 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.
In 2016, Padmanabhan et al retrospectively analyzed 377 eyes of 336 patients (mean age, 15 years) who underwent CXL for progressive keratoconus.\(^{17}\) There was a significant improvement in mean BSCVA from 0.33 to 0.27 logMAR \((p<0.05)\). The authors concluded that the benefits of CXL in stabilizing keratoconus are maintained for longer than 2 years in a majority of pediatric eyes.

In 2008, Raiskup-Wolfe et al reported outcomes of 241 eyes (130-272 patients) treated with CXL, with a minimum of 6 months of follow-up.\(^{18}\) 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 \((K_{\text{max}})\) 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 \((n=33)\), \(K_{\text{max}}\) 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.\(^{19}\) Mean patient age at the time of treatment was 28 years \((\text{range, 14-42 years})\). 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 after 5 years and one after 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 2010 publication from the Siena Eye Cross Study reported a 52-month mean follow-up \((\text{range, 48-60 months})\) on their first 44 keratoconic eyes treated with CXL.\(^{20}\) Follow-up evaluations were performed at 1, 2, 3, 6, 12, 24, 36, 48, and 60 months after CXL. Topographic analysis showed the following mean \(K\) reading reductions: \(-1.96\) 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 2012 publication from the Siena CXL Pediatrics trial reported 12- to 36-month follow-up after CXL in 152 patients aged 18 years or younger with keratoconus progression.\(^{21}\) Visual acuity increased by an average of 0.15 Snellen lines, whereas a clinically relevant change is generally considered to be 2 Snellen lines.

The French National Reference Center for Keratoconus published their findings in 2011.\(^{22}\) 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 \(K_{\text{max}}\) 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 is limited by the 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. 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 of these adverse reactions resolve in the first month, while others can take up to 12 months to resolve. However, in 1% to 6% of patients these adverse reactions may continue up to or beyond 12 months.

**SUMMARY OF EVIDENCE**
For individuals who have progressive keratoconus who receive 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 the Kmax by 1 diopter was achieved at month 3 and maintained at months 6 and 12, compared to sham controls. The sham-controlled reduction in Kmax was 1.9 and 2.3 D with CXL treatment in patients with keratoclonus respectively in the 2 RCTs. Long-term follow-up for visual acuity outcomes are needed. The adverse events associated with this procedure include corneal opacity (haze), corneal epithelial defects, and other ocular findings. Most of these adverse events resolve in the first month but, in a few (1%-6%) patients, may continue for 6 to 12 months. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received 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 U.S. Food and Drug Administration (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

National Institute for Health and Care Excellence
In 2013 the National Institute for Health and Care Excellence (NICE) issued guidance on corneal collagen cross-linkage (CXL) using riboflavin and ultraviolet that updated and replaced its 2009 guidance.(26) 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.

MEDICARE NATIONAL COVERAGE
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
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<td></td>
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<tr>
<td>NCT01972854a</td>
<td>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</td>
<td>206</td>
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<tr>
<td>NCT00560651</td>
<td>German Corneal Cross-Linking Registry</td>
<td>7500</td>
<td>Nov 2017</td>
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<td>NCT01604135</td>
<td>Collagen Crosslinking for Keratoconus - a Randomized Controlled Clinical Trial</td>
<td>200</td>
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<tr>
<td><strong>Unpublished</strong></td>
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<tr>
<td>NCT01459679</td>
<td>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</td>
<td>4000</td>
<td>Jan 2016 (terminated)</td>
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<tr>
<td>NCT01344187a</td>
<td>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</td>
<td>236</td>
<td>Jun 2016 (completed)</td>
</tr>
</tbody>
</table>

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

References


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0402T</td>
<td>Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed)</td>
</tr>
</tbody>
</table>

**ICD10 Codes**

- H18.601- H18.629 Keratoconus code range
- H18.711- H18.719 Corneal ectasia code range

Effective in 2016, there is a specific CPT category III code for this service:
0402T: Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed)

Prior to 2016, there were no specific CPT codes for this treatment. It would have been reported using CPT code 66999 - unlisted procedure, anterior segment of eye.

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

- 5/1/16 New Policy; considered investigational.
- 5/1/17 Policy statements changed to (1) corneal collagen cross-linking using riboflavin and ultraviolet A may be considered medically necessary as a treatment of progressive keratoconus and corneal ectasia after refractive surgery, and (2) corneal collagen cross-linking using riboflavin and ultraviolet A is considered investigational for all other indications.