**Corneal Collagen Cross-linking**

**Policy #** 00325  
**Original Effective Date:** 12/21/2011  
**Current Effective Date:** 11/16/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

*Note: Implantation of Intrastromal Corneal Ring Segments is addressed separately in medical policy 00164.*

**Services Are Considered Investigational**  
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers corneal collagen cross-linking (CXL) for all indications to be investigational.*

**Background/Overview**

Corneal collagen cross-linking is a photochemical procedure that is being evaluated as a method to stabilize the cornea in patients with progressive keratectasia such as keratoconus and pellucid marginal degeneration. Corneal collagen cross-linking may also have anti-edematous and antimicrobial properties.

Corneal collagen cross-linking is performed with the photosensitizer riboflavin (vitamin B2) and ultraviolet-A (UVA) irradiation. A common CXL protocol removes about 8 mm of the central corneal epithelium 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 UVA, a maximal wavelength for absorption by riboflavin, together with the continued application of riboflavin. The interaction of riboflavin and UVA causes the formation of reactive oxygen species, leading to additional covalent bonds (cross-linking) between collagen molecules that results 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, and retina) are not exposed to a UV dose that above the cytotoxic threshold.

Keratoconus is a bilateral dystrophy that is characterized by progressive ectasia (paracentral steepening and stromal thinning) that impairs visual acuity. The progression of keratoconus is highly variable. 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 LASIK, but in general, results of these techniques have been poor. Implantation of intrastromal corneal ring segments (ICRS) is an additive technique in which the implants are intended to reinforce the cornea, prevent further deterioration, and potentially obviate the need for a penetrating keratoplasty. A penetrating keratoplasty (i.e., 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, CXL has the potential to slow the progression of disease.
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Pellucid marginal degeneration is a noninflammatory progressive degenerative disease, typically characterized by bilateral peripheral thinning (ectasia) of the inferior cornea. Deterioration of visual function results from the irregular astigmatism induced by asymmetric distortion of the cornea, and visual acuity typically cannot be restored by using spherocylindrical lenses. Rigid gas permeable contact lenses may be used to treat pellucid marginal degeneration. Intrastromal ring segment implantation, crescentic lamellar keratoplasty, penetrating keratoplasty, and corneal wedge excision have also been proposed.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
No UVA devices have received clearance or premarket approval for the treatment of keratoconus in the U.S. A search of clinicaltrials.gov shows ongoing Phase 3 safety and efficacy trials of UV-A Illumination Systems by Topcon Medical (VEGA) and Avedro Inc. (KXL or UV-X). The FDA has granted Avedro a priority review of their new drug application (NDA) for the riboflavin ophthalmic solution/KXL II™ system as an orphan drug (<200,000 individuals affected in the U.S.). If approved, Avedro would have 7 years of market exclusivity in the U.S. In October 2015, Avedro resubmitted its NDA to FDA. The KXL II system is currently approved for use in Europe.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination.

Rationale/Source
Natural History of Keratoconus
The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study is a multi-center long-term observational study of the natural history of keratoconus. Two reports were published from the CLEK study in 2006 that showed slow changes over 7 years of follow-up. Davis et al reported changes in high- and low-contrast visual acuity from 953 patients (1855 eyes). Over a period of 7 years, there was a decrease of 2 high- and 4 low-contrast letters. High-contrast visual acuity decreases of > 10 letters occurred in 19.0% of patients; low-contrast visual acuity decreases of > 10 or more letters occurred in 30.8% of patients. McMahon et al. reported longitudinal changes in corneal curvature over 8 years of follow-up in 1032 patients. The slope for First Definite Apical Clearance Lens (FDACL) was 0.18 diopters (D) per year, and the slope for flatter keratometric reading (Flat K) was 0.20 D per year. These translated into mean increases of 1.44 D in FDACL and 1.6 D in Flat K. during the 8-year follow-up period. Close to 25% of patients had projected increases of 3 D or more in FDACL while 24% had projected increases of 3 D or more in Flat K.

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Evidence on whether CXL improves health outcomes for patients with progressive keratoconus includes 5 randomized controlled trials (RCTs), 3 of which were regulated by the FDA under a NDA. In addition, there are a number of prospective controlled studies as well as uncontrolled trials that report on longer-term outcomes of the procedure. The main health outcome for CXL treatment is improvement, or stabilization, of visual acuity. Other outcomes commonly reported in trials of CXL include physiologic measures, such as the steepness of the corneal curvature measured by maximum keratometry (K-max) and/or the manifest refraction spherical equivalent (MRSE). These are intermediate outcomes that may corroborate whether improvements in visual acuity correlate with physiologic changes.
Randomized Controlled Trials

Data submitted to FDA under the NDA for riboflavin ophthalmic solution/KXL came from 3 RCTs with a total sample size of 640 patients. Results from one of the trials were published in 2011 and 2012. Each of the phase 3 trials was a parallel group, open-label trial in patients with keratoconus or corneal ectasia due to LASIK or photorefractive keratectomy. 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 UVA light source turned on. The primary outcome was a 1 D difference in the mean change in K-max (progression of steepening) between the CXL and control groups at 12 months. Control patients could cross over to CXL at 3 months, and missing data were analyzed by last observation carried forward (LOCF). Ninety-nine percent of control patients had crossed over by 12 months. Last observation carried forward analysis is a conservative method of analysis in this situation, because it reduces the expected worsening over time in untreated patients. In the pooled analysis of patients with keratoconus, steepening worsened by 1.0 D in the control group and improved by 1.6 D in the CXL group, for a total difference between groups of 2.6 D. CXL resulted in either stabilization or improvement in K-max in 72% of keratoconus patients. In the sham control group, there was no statistically significant change in K-max. The mean improvement in best-corrected visual acuity (BCVA) was 5.6 letters following CXL compared with 2.0 letters for controls (p=0.009). Although this difference is not typically considered clinically significant, it is limited by the use of 3-month data for many of the patients in the control group, which would minimize between-group differences over time. The proportion of patients who had a clinically significant 3-line or greater improvement in BCVA was 19.4% for the CXL-treated patients and 8.1% for controls. Treatment-related adverse events were generally transient, mild, and expected based on the epithelial débridement and corneal remodeling.

Wittig-Silva et al reported the first RCT of corneal CXL in 2008. Three-year results were published in 2014. 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 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 1.00 D in the steepest simulated keratometry reading (K-max); an increase in astigmatism determined by manifest subjective refraction of at least 1.00 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 K-max by -1.03 D, compared with an increase in K-max of 1.75 in the control group. One eye in the CXL group progressed by more than 2.0 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 and there was a trend of a decrease in BCVA (p=0.10). The difference between groups in UCVA was statistically significant. Follow-up is continuing through 5 years.

In 2012, Renesto et al reported 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 ICRS. Patients were evaluated at 1 and 3 months after treatment with CXL or riboflavin, and then at 1, 3, 6, 12,
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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

**Uncontrolled Studies**

Longer term follow-up is being reported from Europe, where the procedure 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 for new contact lens-fitting more than once in 2 years. The largest and longest series to date are described next.

In 2008, Raiskup-Wolfe et al reported outcomes of 241 eyes (130 patients) treated with CXL, with a minimum of 6 months of follow-up. This was of a total of 488 eyes (272 patients) with progressive keratoconus and a corneal thickness of at least 400 μm treated at their center in Germany. 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.11 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 2010 publication from the Siena Eye Cross Study reported a 52-month mean follow-up (range, 48-60) on their first 44 keratoconic eyes treated with CXL. 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 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. Visual acuity increased by an average of 0.15 Snellen lines, whereas a clinically relevant change is generally considered to be 2 Snellen lines.

One of the oldest reports is from the French National Reference Center for Keratoconus in 2011. 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
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40%, and decreased in 12%. Keratoconus progression had stopped in 69%, and K-max had decreased by more than 2.0 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 more than 2 Snellen lines of visual acuity. This retrospective study is limited by the low proportion of patients available at 12-month follow-up.

Adverse Events
Reported adverse events are relatively uncommon, but precise rates of adverse events are not available because of the lack of large studies with long-term follow-up. Adverse events reported to date include corneal endothelial damage, stromal haze, corneal melt, keratitis, gaping of corneal incisions, and corneal scarring.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy 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>
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<td><strong>Ongoing</strong></td>
<td>A Randomized, Controlled Study of the Vedera™‡ KXS Microwave System With Corneal Collagen Cross-Linking Compared With Corneal Collagen Cross-Linking Alone for Eyes With Keratoconus</td>
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<td>Aug 2017</td>
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<td>NCT01672814</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>
<td>Mar 2016</td>
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<td>NCT01972854</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>226</td>
<td>Dec 2016</td>
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<tr>
<td>NCT01344187</td>
<td>Collagen Crosslinking for Keratoconus - a Randomized Controlled Clinical Trial</td>
<td>200</td>
<td>May 2017</td>
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<tr>
<td>NCT01604135</td>
<td>German Corneal Cross-Linking Registry</td>
<td>7500</td>
<td>Nov 2017</td>
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<td><strong>Unpublished</strong></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>
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NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial.

Summary
The evidence for corneal CXL in individuals who have keratoconus includes RCTs and systematic reviews. Relevant outcomes are change in disease status, functional outcomes, and treatment related morbidity. There is evidence from RCTs, including several pivotal trials, that CXL leads to short-term improvements in corneal steepening and visual acuity compared with untreated eyes, and results from 1 trial have reported that benefits are maintained at 2 to 3 years. From these RCTs, one can conclude that CXL is able to...
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reduce, and in some cases reverse, the corneal steepening that leads to a reduction in visual acuity in the short-term. There is greater uncertainty about the long-term outcomes of CXL for the treatment of keratoconus. Some retrospective studies report positive outcomes at out to 10 years, although these reports are limited by the small sample size at long-term follow-up and limited information on the entire population of patients treated with CXL during the same time period. There is a need for prospective studies with larger numbers of patients that are followed over many years to determine whether CXL improves longer term outcomes. Several trials are ongoing, and results from these other trials are expected soon. Longer term outcomes from large cohorts will also be useful to evaluate potential long-term complications of this new treatment approach. Although one device is currently under FDA review, no CXL devices have received FDA approval at this time. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

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Policy History

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<th>Date</th>
<th>Action Description</th>
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<td>12/08/2011</td>
<td>Medical Policy Committee review</td>
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<td>12/06/2012</td>
<td>Medical Policy Committee review</td>
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<td>12/19/2012</td>
<td>Medical Policy Implementation Committee approval. No change to coverage.</td>
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<td>11/07/2013</td>
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<tr>
<td>08/03/2015</td>
<td>Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.</td>
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<td>10/29/2015</td>
<td>Medical Policy Committee review</td>
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<td>11/16/2015</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
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<td>11/03/2016</td>
<td>Medical Policy Committee review</td>
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<td>01/01/2017</td>
<td>Coding update: Removing ICD-9 Diagnosis Codes</td>
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Next Scheduled Review Date: 11/2017

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
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<tr>
<td>HCPCS</td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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