BlueCross BlueShield of Louisiana

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Corneal Collagen Cross-linking

Policy # 00325
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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.

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 and has been evaluated for the treatment of bullous keratopathy and infectious keratitis.

Corneal collagen cross-linking is performed with the photsensitizer 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 photsensitizer 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.

Corneal collagen cross-linking is being evaluated primarily for corneal stabilization in patients with progressive corneal thinning such as keratoconus. Corneal collagen cross-linking 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. 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.

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 III safety and efficacy trials of UV-A Illumination Systems by Topcon Medical (VEGA) and Avedro Inc. (KXL or UV-X).

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.

Evidence Review

Does Corneal Cross-linking improve health outcomes for patients with progressive keratoconus?
The evidence on this question consists of 3 controlled trials, 2 of which are randomized. In addition, there are 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 and/or the manifest refraction spherical equivalent (MRSE). These are intermediate outcomes that may corroborate whether improvements in visual acuity correlate with physiologic changes, and which may or may not be adequate surrogates for true health outcomes.

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Controlled Trials
Wittig-Silva and colleagues reported the first randomized controlled trial (RCT) of CXL in 2008. At the time of analysis, 66 eyes of 49 patients with progression of keratoconus had been enrolled. To be eligible for enrollment, clear evidence of progression of the ectasia over the preceeding 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, 30 eyes had been treated with CXL with follow-up available on 24 eyes at 3 months, 17 at 6 months, and 9 at 12 months (follow-up will continue annually for 5 years). Out of the 33 eyes randomized to the control group, 23, 17, and 11 had completed 3, 6, and 12-month follow-up, respectively.

There was a trend toward improvement of best-corrected visual acuity (BCVA) in treated eyes, with an average improvement of -0.01 logMAR [logarithm of the minimum angle of resolution] at 3 months, -0.07 logMAR at 6 months, and -0.12 logMAR at 12 months ($p = 0.07$). In the control group, BCVA was significantly decreased at 12 months. Corneal collagen cross-linking treated eyes showed a significant flattening of K-max at 3, 6, and 12 months (-0.74 D, -0.92 D, -1.45 D, respectively), while K-max increased significantly at 3, 6, and 12 months in the control group (0.60 D, 0.60 D, and 1.28 D, respectively). No significant changes were observed in the refractive sphere, astigmatism, and MRSE values in either group. A limitation of this study is that only one-third of enrolled patients had completed 12-month follow-up, and the results are considered preliminary. Follow-up in a larger number of patients and for a longer duration of time is reported to be continuing.

One-year outcomes of a crossover RCT were reported in 2011 from an FDA-regulated multi-center trial of the UV-X system (IROC). Included in the study were 71 eyes of 58 patients 14 years of age or older with a diagnosis of progressive keratoconus or corneal ectasia, an inferior-superior ratio greater than 1.5 on topography mapping, and a BCVA worse than 20/20. If the cornea was thinner than 400 microns, hypotonic riboflavin was administered to swell the stroma. Patients were randomized to CXL or a control treatment consisting of 60 minutes of topical riboflavin alone with the light not turned on. Patients were aware of the treatment assignment, and the control patients crossed over to CXL treatment after the 3 month follow-up visit. With CXL, BCVA improved significantly at the 3, 6, and 12 month follow-up visits (from 20/45 at baseline to 20/34 at 12 months). There was a significant decrease in the maximum, average, flat, and steep K values during follow-up. Manifest astigmatism and MRSE did not change significantly. In the control group, there were no statistically significant changes in BCDVA, manifest astigmatism, MRSE, maximum, average or steep K values or corneal astigmatism at the 1-month and 3-months follow-up. A limitation of this trial is that the study design does not allow comparison of CXL and sham treatment over longer than 3 months.

In 2012, another publication from the randomized crossover trial described above reported on subjective visual function. There were a total of 107 eyes (76 patients) with progressive keratoconus (n = 71) or corneal ectasia (n = 36). At 1 year after CXL, there were significant improvements in reading difficulty, diplopia, halo, and foreign body sensation in the keratoconus group. There was little to no correlation between the subjective and objective measures of vision and keratoconus progression. In addition to the

limitation created by controls crossing over to active treatment after 3 months, there is a strong potential for bias in subjective measures when participants are not masked to treatment condition.

Also in 2012, Renesto et al. reported results of a randomized trial that compared CXL versus 1 month of riboflavin eyedrops 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, and 24 months after ICRS insertion. There was no significant difference between the 2 groups for uncorrected visual acuity (UCVA), BCVA or in 3 topographic parameters (flattest-K, steepest K, and average keratometry) throughout the 24 months of follow-up.

Coskunseven and colleagues reported a within subject comparison of CXL in 38 eyes of 19 patients with progressive keratoconus in 2008. The eye of each patient that progressed more in the previous 6 months was treated with CXL, while the fellow (other) eye served as the control. At baseline, the treated eyes showed worse UCVA and BCVA, higher spherical equivalent refraction, cylinder, and maximal curvature (K-max), and lower pachymetry. Intraocular pressure (IOP) and endothelial cell count did not differ significantly between the treated and untreated eyes. At 9-months follow-up, CXL-treated eyes showed a significant decrease (less myopic) in spherical equivalent refraction (-1.03 D) cylinder (-1.04 D) and K-max (-1.57 D); these measures did not change significantly in untreated eyes (-0.03 D, -0.01 D and +0.04 D, respectively). Uncorrected visual acuity and BCVA increased in CXL-treated eyes (+0.06 and +0.10, respectively) and decreased in untreated eyes (-0.08 and -0.06, respectively). There was an increase in IOP from 9 to 11 mm Hg in CXL-treated eyes.

Uncontrolled Studies
In 2008, Raiskup-Wolf and colleagues reported outcomes of 241 eyes (130 patients) treated with CXL, with a minimum of 6 months follow-up. This was out of a total of 488 eyes (272 patients) with progressive keratoconus and a corneal thickness of at least 400 microns treated at their center in Germany. Progression was indicated by either an increase in maximum K of 1.00 D in 1 year, patient report of deteriorating visual acuity, or the need for new contact lens fitting more than once in 2 years. Follow-up examinations were performed at 1, 6, and 12 months, and then annually. The 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. This study is limited by the retrospective nature of the study and the low number of cases with extended follow-up.

Twelve-month results from 142 eyes treated with CXL from the French National Reference Center for Keratoconus were reported in 2011. Inclusion criteria for this retrospective study were confirmed keratoconus, central corneal thickness greater than 400 microns, disease progression proven by previous central keratometry reports, and subjective loss of vision (loss of > 2 lines in 1 year or keratometry increasing more than 1.0 D in 6 months or 2.0 D in 12 months). Stable visual acuity was defined as a 1-line change in BCVA, improvement was defined as a 2-line gain of BCVA, and failure was a 2-line loss in BCVA. Progression was defined as an increase of more than 1.0 D in K-max in 6 months or of more than 2.0 D in 12 months. Out of 142 eyes enrolled in the study, 6-month follow-up was available for 104 (73.2%), and 12-

month follow-up was available for 64 (45.1%). At 12 months after treatment, the BCVA had stabilized in 31 of the 64 eyes (47.6%), improved in 26 eyes (40%) and decreased in 8 eyes (12%). Keratoconus progression had stopped in 42 eyes (68.8%), and the K-max value had decreased by more than 2.0 D in 13 eyes (21.3%). 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. Indicators of failure were preoperative K-max greater than 58.0 D, age older than 35 years, and female gender. This retrospective study is also limited by the low percentage of patients available at 12-month follow-up.

A 2010 publication from the Siena Eye Cross Study reported a 52.4 month mean follow-up (range 48 to 60 months) on their first 44 keratoconic eyes treated with CXL. Included in the study were 44 patients between 10 and 40 years of age with disease progression in the previous 6 months, minimum corneal thickness of 400 microns in the thinnest point, topographic mean K value < 55 D, clear cornea by slit-lamp examination, and absence of eye infections, herpetic clinical history, autoimmune disease, and pregnancy. 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. In 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 IOP over follow-up. Temporary side effects included stromal edema in the first 30 days (70% of patients) and temporary haze (9.8% of patients). No persistent side effects were observed.

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 stromal haze, corneal melt, keratitis, and corneal scarring.

Ongoing Clinical Trials
A search of clinicaltrials.gov in September 2011 identified a number of ongoing studies of CXL for keratoconus. Sham-controlled trials include:

- An industry-sponsored multi-center sham controlled trial of the KXL system with riboflavin (NCT01344187). The study will evaluate the change in maximum corneal curvature at 6 and 12 months after active and sham treatment. The study began August 2011, has an estimated enrollment of 340 patients, and a completion date of December 2013.
- An industry-sponsored multi-center sham controlled trial of the VEGA UVA system with riboflavin (NCT01190306). The primary outcome measure is the change in corneal curvature in the 2 groups at 6 months. The study has an estimated enrollment of 120 patients with completion in April 2012.
- A randomized comparison of CXL or sham in 150 patients with keratoconus (NCT00841386). The primary outcomes are BCVA, corneal curvature, and power of the cornea at 24 months. The estimated study completion date is December 2011.
- A randomized comparison of CXL or sham in 130 patients with keratoconus (NCT00626717). The primary outcome measures are keratoconus progression and endothelial cell loss at 3 years. The estimated study completion date is December 2012.

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Also identified on clinicaltrials.gov is the German Corneal Cross-Linking Registry (NCT00560651). Goals of the registry are to gather long-term results of CXL, detect rare complications and side effects, and evaluate efficacy in a large number of patients. There is an estimated enrollment of 7500 patients with a study completion date of November 2012.

Summary
Corneal cross-linking is a treatment for progressive keratoconus and other forms of corneal ectasia. No CXL devices have received FDA approval for this indication. There is evidence from small RCT's that corneal cross-linking may lead to short-term improvements in visual acuity compared to untreated eyes. However, due to the variable natural history of keratoconus, there is a need for prospective randomized controlled trials with a large number of patients that are followed over many years to determine whether CXL improves longer-term outcomes. Several trials are ongoing, and 2 to 3-year results are expected soon. Longer-term outcomes from large cohorts are also needed to evaluate potential complications of this new treatment approach. Therefore, CXL is considered investigational.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Corneal Collagen Cross-linking", 9.03.28, 03:2013.
2. Davis LJ, Schechtman KB, Wilson BS et al. Longitudinal changes in visual acuity in keratoconus. Invest Ophthalmol Vis Sci 2006; 47(2):489-500.
3. McMahon TT, Edrington TB, Szczotka-Flynn L et al. Longitudinal changes in corneal curvature in keratoconus. Cornea 2006; 25(3):296-305.
4. 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.
5. 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.
6. Brooks NO, Greenstein S, Fry K et al. Patient subjective visual function after corneal collagen crosslinking for keratoconus and corneal ectasia. J Cataract Refract Surg 2012; 38(4):615-9.
7. 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.
8. Coskunseven E, Jankov MR, 2nd, Hafezi F. Contralateral eye study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus. J Refract Surg 2009; 25(4):371-6.
9. 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.
10. 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.
11. 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.
12. Caporossi A, Mazzotta C, Baiocchi S et al. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. Cornea 2012; 31(3):227-31.
13. Gkika M, Labiris G, Kozobolis V. Corneal collagen cross-linking using riboflavin and ultraviolet-A irradiation: a review of clinical and experimental studies. Int Ophthalmol 2011; 31(4):309-19.
14. Gokhale NS. Corneal endothelial damage after collagen cross-linking treatment. Cornea 2011; 30(12):1495-8.
15. Abad JC, Vargas A. Gaping of radial and transverse corneal incisions occurring early after CXL. J Cataract Refract Surg 2011; 37(12):2214-7.
16. National Institute for Health and Clinical Excellence (NICE). Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus. 2009. Available online at: http://www.nice.org.uk/nicemedia/live/12119/46253/46253.pdf.
17. National Keratoconus Foundation. Crosslinking. Available online at: http://www.nkcf.org/crosslinking/.

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Code Type	Code
CPT	66999
HCPCS	No code
ICD-9 Diagnosis	371.60, 371.71
ICD-9 Procedure	No code

Policy History

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12/08/2011 Medical Policy Committee review
12/21/2011 Medical Policy Implementation Committee approval. New policy.
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12/19/2012 Medical Policy Implementation Committee approval. No change to coverage.
11/07/2013 Medical Policy Committee review
11/20/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 11/2014

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A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (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:

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