Corneal Collagen Cross-linking

Policy # 00325
Original Effective Date: 12/21/2011
Current Effective Date: 11/15/2017

 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.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider corneal collagen cross-linking (CXL) using riboflavin and ultraviolet A (UVA) as a treatment of progressive keratoconus or corneal ectasia after refractive surgery in patients who have failed conservative treatment (e.g., spectacle correction, rigid contact lens) to be eligible for coverage.

When 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) using riboflavin and ultraviolet A (UVA) for all other indications to be investigational*.

Policy Guidelines
Corneal collagen cross-linking (CXL) may be considered eligible for coverage when at least one of the following criteria is met:
- An increase of 1 diopter (D) in the steepest keratometry value;
- An increase of 1 diopter (D) in regular astigmatism evaluated by subjective manifest refraction;
- A myopic shift (decrease in the spherical equivalent) of 0.50 diopter (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.

Background/Overview
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). 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 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 LASIK, although generally, results of these techniques have been poor. Implantation of intrastromal corneal ring segments [ICRS] (see medical policy 00164) 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 (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.

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.

CXL has the potential to slow the progression of disease. It is performed with the photosensitizer riboflavin (vitamin B_2) and 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 UVA 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.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration

In 2016, riboflavin 5’-phosphate in 20% dextran ophthalmic solution (Photrex® Viscous; Avedro) and riboflavin 5’-phosphate ophthalmic solution (Photrex®; Avedro) were approved by the U.S. FDA for use with KXL System in CXL for the treatment of progressive keratoconus and corneal ectasia after refractive surgery.

Centers for Medicare and Medicaid Services (CMS)

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

**Rationale/Source**

**CORNEAL COLLAGEN CROSS-LINKING FOR KERATOCONUS AND ECTASIA**

**Pivotal Trials**

The evidence base for FDA approval of epi-off 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. These RCTs are summarized in the next section.

The 3 open-label RCTs are summarized in Table 1. The primary end point was a 1-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 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 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Design</th>
<th>Dates</th>
<th>Patients (N or n)</th>
<th>Difference in Mean Change in Kmax From Baseline to 12 Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpublished</td>
<td>UVX-001</td>
<td>RCT</td>
<td>2008-2010</td>
<td>Keratoconus (58)</td>
<td>-1.9 D (-3.4 to -0.3)</td>
</tr>
<tr>
<td>Hersh (2011)</td>
<td>UVX-002</td>
<td>RCT</td>
<td>2008-2010</td>
<td>Keratoconus only (147)</td>
<td>-2.0 D (-3.0 to -1.1)</td>
</tr>
<tr>
<td>Hersh (2011)</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 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 value 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 or in FDA documents. 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 Photrex and Photrex Viscous do not include any visual acuity outcomes.

Table 2. Summary of Results for Visual Acuity 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 Eye:</td>
<td>Sham-Controlled Eyes</td>
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<tr>
<td>UVX-001</td>
<td>Keratoconus (58)</td>
<td>+7.2</td>
<td>+3.4</td>
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<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>UVX-003</td>
<td>Ectasia only (130)</td>
<td>+5.0</td>
<td>-0.1</td>
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<tr>
<td>Pooled</td>
<td>Keratoconus (205)</td>
<td>+5.6</td>
<td>+2.0</td>
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<tr>
<td></td>
<td>Ectasia (179)</td>
<td>+5.0</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

Table 3. Summary of Results for Visual Acuity Outcomes in the Pivotal Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N or n)</th>
<th>Difference From Baseline to 12 Months in Percent Patients Who Gained ≥15 Letters on ETDRS</th>
<th>Differencea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CXL-Treated Eye:</td>
<td>Sham-Controlled Eyes</td>
</tr>
<tr>
<td>UVX-001</td>
<td>Keratoconus (58)</td>
<td>+24.1%</td>
<td>+21.4%</td>
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<tr>
<td></td>
<td>Ectasia (49)</td>
<td>+21.7%</td>
<td>+4.2%</td>
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<tr>
<td>UVX-002</td>
<td>Keratoconus only (147)</td>
<td>+17.4%</td>
<td>+2.8%</td>
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<tr>
<td>UVX-003</td>
<td>Ectasia only (130)</td>
<td>+9.2%</td>
<td>+4.8%</td>
</tr>
<tr>
<td>Pooled</td>
<td>Keratoconus (58)</td>
<td>19.4%</td>
<td>8.1%</td>
</tr>
<tr>
<td></td>
<td>Ectasia (49)</td>
<td>12.5%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

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

Other Randomized Controlled Trials

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 were randomized to CXL treatment and 50 eyes 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 was 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 2010, Renesto et al reported 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. After 3 months, all patients received ICRS (see medical policy 00164). 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 were no significant differences 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 was conducted in August 2014 and did not include all of the phase 3 trials that were submitted to 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.

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 appeared to be effective at halting the deterioration of keratoconus, it was only slightly effective at improving visual acuity.

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 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**

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. 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.

In 2008, Raiskup-Wolf et al reported outcomes of 241 eyes (272 patients) treated with CXL, with a minimum of 6 months of follow-up. 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 (Kmax) 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), Kmax 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. Mean patient age at the time of treatment was 28 years (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 their retrospective designs and the small number of cases with extended follow-up.

A 2010 publication from the Siena Eye Cross Study reported 52-month mean follow-up (range, 48-60 months) for 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 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 ages 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.

The French National Reference Center for Keratoconus published their findings 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 40%, and decreased in 12%. Keratoconus progression had stopped in 69%, and Kmax 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 the 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 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 CXL using riboflavin and UVA, 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 maximum corneal curvature (Kmax) by 1 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 UVA, 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.

References


Policy History
Original Effective Date: 12/21/2011
Current Effective Date: 11/15/2017
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12/06/2012 Medical Policy Committee review

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12/19/2012 Medical Policy Implementation Committee approval. No change to coverage.
11/07/2013 Medical Policy Committee review
11/06/2014 Medical Policy Committee review
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review
11/15/2017 Medical Policy Implementation Committee approval. Coverage changed from investigational to eligible for coverage. Added that corneal collagen cross-linking using riboflavin and ultraviolet A may be considered eligible for coverage as a treatment of progressive keratoconus and corneal ectasia after refractive surgery. Added that corneal collagen cross-linking using riboflavin and ultraviolet A is considered investigational for all other indications. Added BCBSA Policy Guidelines section.

Next Scheduled Review Date: 11/2018

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

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<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
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<tr>
<td>CPT</td>
<td>0402T, 66999</td>
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<td>HCPCS</td>
<td>No codes</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 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:

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.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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