Corneal Cross-Linking

Medical Policy #: 07.01.72
Original Effective Date: September 2016
Reviewed: September 2021
Revised: September 2021

DESCRIPTION

Corneal cross-linking (CXL) is an in-office eye procedure that is said to strengthen or stabilize the cornea if it's been weakened by keratoconus or corneal ectasia after refractive surgery.

- Keratoconus is a dystrophy of the cornea characterized by progressive deformation (steepening) of the cornea.
- Corneal ectasia is keratoconus that occurs *after refractive surgery*.

Both lead to functional loss of vision and need for corneal transplantation.

Progressive keratoconus may be defined by measurement of at least one of the following:

- An increase of 1 D (diopter) in the steepest keratometry value
- An increase of 1 D (diopter) in regular astigmatism evaluated by subjective manifest refraction
- A myopic shift (decrease in the spherical equivalent) of 0.50 D (diopter) 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.

According to the Global Consensus on Keratoconus and Ectatic Diseases: abnormal posterior ectasia, abnormal corneal thickness distribution and clinical noninflammatory corneal thinning must be present for a diagnosis of keratoconus. "Ectasia progression" is defined by a consistent change in at least two of the following parameters:

- Steepening of the anterior corneal surface
- Steepening of the posterior corneal surface
- Thinning and/or an increase in the rate of corneal thickness change

Typically, standard conservative treatment will be attempted prior to CXL such as one or more the following:

- Spectacles
- Contact lenses
- Intracorneal ring segments (ICRS)

During the CXL procedure, riboflavin is applied to the epithelized or de-epithelialized cornea followed by exposure to UV light. Using riboflavin as a photosensitizer and ultraviolet-A (UVA) to increase the formation of intra and interfibrillar covalent bonds by photosensitized oxidation thus, resulting in a measurable stiffening of corneal tissue. This treatment has also been used to treat infectious corneal ulcers and in combination with other treatments, such as intracorneal ring segment implantation. CXL may also have anti-edematous and antimicrobial properties.

- Alternative and brand names for the procedure include corneal crosslinking, corneal collagen crosslinking, C3-R, CCL and KXL.

In review: The two basic types of corneal cross-linking are:

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

The expected result is that the progression of keratoconus stops or is slowed. CXL does not reverse keratoconus changes that have already occurred and is recommended for

those who are recently diagnosed and whose keratoconus is progressing. The procedure is less impactful for those who are no longer experiencing vision changes due to keratoconus.

PICO:
The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with progressive keratoconus and ectasia.

Intervention
The treatment being considered is corneal collagen cross-linking with riboflavin and ultraviolet A irradiation, which is performed by an ophthalmologist in an outpatient clinical setting.

Patients with progressive keratoconus and ectasia are actively managed by an ophthalmologist.

Comparators
The comparators of interest are observation, rigid or specialty contact lens, intracorneal ring segments, or corneal transplant. About 20% of patients with keratoconus will require corneal transplantation.

Patients with progressive keratoconus and ectasia are actively managed by an ophthalmologist. Corneal transplant is performed by an ophthalmologist or ophthalmologic surgeon.

Outcomes
The outcomes of interest are change in disease status, functional outcomes, and treatment-related morbidity. Positive outcomes include slowing of disease progression and improvement in visual acuity and other ocular measurements. None of the currently available treatment options for keratoconus reverse the progression of disease. Negative outcomes include infection, adverse reactions, and need for alternative treatment, including corneal transplant.

Follow-up of at least one year is needed to assess outcomes.

Literature: Ectasia
(2017) Hersh et al compared topographical with visual outcomes of 179 patients treated for corneal ectasia following laser in situ keratomileusis or photorefractive keratectomy surgery. The prospective, multicenter controlled trial randomized 91 patients to treatment with standard corneal collagen cross-linking and 88 patients to a sham procedure which administered riboflavin alone and did not require the removal of the epithelium. The primary endpoint was a 1-year change in maximum corneal curvature, which was a mean 0.7-D decrease in the corneal collagen cross-linking group and a 0.6-D increase in the

control group (between-group difference, 1.3 D; p<0.001). A significantly greater improvement in corrected distance visual acuity was observed for the corneal collagen cross-linking group (5.0 logMAR gained) than for the control group (0.3 logMAR lost; p<0.001), as was the case with uncorrected distance visual acuity, for which the between-group difference was 4.6 letters (p<0.001). There was no significant difference between treatment and control groups for either manifest refraction spherical equivalent myopia or endothelial cell density, and fewer than 5% of eyes had adverse events. Over half of patients (68%) reported corneal stromal haze or demarcation line. The trial was limited by the last observation carried forward analysis required for the control patients who elected to receive treatment after 3 months; also, because only 4 patients received photorefractive keratectomy surgery, comparison between types of surgery and effects of postsurgery corneal collagen cross-linking were precluded.

(2008) Wittig-Silva et al reported the first RCT of corneal collagen cross-linking. Three-year results were published in 2014.21, Recruitment for the trial was completed in 2009 with 50 eyes randomized to corneal collagen cross-linking treatment and 50 eyes to the 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 was met: an increase of at least 1 D in the steepest simulated maximum corneal curvature; 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 corneal collagen cross-linking treated and 48 control eyes. Last observation carried forward was used for 26 eyes, including 17 eyes from the control group with a progressive disease that underwent compassionate-use corneal collagen cross-linking or corneal transplantation. In the corneal collagen cross-linking group, there was a flattening of maximum corneal curvature by -1.03 D, compared with a 1.75 increase in maximum corneal curvature in the control group. One eye in the corneal collagen cross-linking group progressed by more than 2 D, compared with 19 eyes in the control group. Uncorrected visual acuity and best-corrected visual acuity improved in the corneal collagen cross-linking treated eyes at 1, 2, and 3 years.

Overall results showed improvement in uncorrected distance visual acuity, corrected distance visual acuity, Best spectacle-corrected visual acuity, and maximum corneal curvature compared to sham after at least 12 months. In addition, a higher proportion of participants in the corneal collagen cross-linking group had a ≥15-letter improvement with best spectacle-corrected visual acuity than in the sham group.

Summary of Evidence: Ectasia

Trials showed significant improvements not only in maximum corneal curvature but also visual acuity measures in the corneal collagen cross-linking groups compared with the control groups. The first and longest trial followed patients up to three years and saw continued improvement in visual acuity with corneal collagen cross-linking. Long-term follow-up for visual acuity outcomes is needed. The adverse events associated with

corneal collagen cross-linking were the same for the ectasia trials as for the keratoconus. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

(2017) McAnena et al, reported on the results of a systematic review and a meta-analysis assessing the efficacy of corneal collagen cross-linking 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 best-corrected visual acuity 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 best-corrected visual acuity remained significant (SMD, -1.03; 95% CI, -2 to -0.06; $p=0.04$).

(2016) Meri et al, reported on the results of a systematic review and meta-analysis of ocular functional and structural outcomes in patients with keratoconus who underwent corneal collagen cross-linking 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 corneal collagen cross-linking. Reviewers concluded that, although

corneal collagen cross-linking appeared to be effective at halting the deterioration of keratoconus, it was only slightly effective at improving visual acuity.

(2015) A Cochrane review evaluated the use of corneal collagen cross-linking for the treatment of keratoconus. The literature search was conducted in August 2014 and did not include all the phase 3 trials 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 because of the risk of bias in the included studies, imprecision, indirectness, and publication bias.

Overall results showed long-term reduction in corneal curvature and less significant improvements in visual acuity, although some studies found significant improvement in best spectacle-corrected visual acuity up to at least two years.

Summary of Evidence: Keratoconus
Several studies measured visual acuity and found significant and lasting improvements in corrected visual acuity and other measures with corneal collagen cross-linking. Long-term follow-up for visual acuity outcomes is needed. The adverse events associated with corneal collagen cross-linking include corneal opacity (haze), corneal epithelial defects, and other ocular findings. Most adverse events resolved in the first month but continued in a few (1%-6%) patients for 6 to 12 months. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence (NICE)
(2013) NICE issued guidance on corneal collagen cross-linking using riboflavin and ultraviolet A, updating its guidance based on a 2009 systematic review of primarily low-quality evidence; review authors declared no financial conflicts of interest. (Accessed September 1, 2021)

- “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…."

(2013) Additionally NICE encourages further research into CXL using riboflavin and UVA for keratoconus and keratectasia, especially **epithelium-on (transepithelial) CXL and the combination (CXL-plus) procedures**. Details of the techniques used should be clearly described. Reported outcomes should include visual acuity, corneal topography and quality of life. Data on long-term outcomes for all types of CXL using riboflavin and UVA for keratoconus and keratectasia would be useful – specifically data about prevention of progression to corneal transplantation and about repeat procedures and their efficacy.

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. (Accessed September 2, 2021).

The Cornea Research Foundation of America

The Cornea Research Foundation of America contributed to the recent USA Food and Drug Administration (FDA) approval of cross-linking for halting or slowing the progression of keratoconus and corneal ectasia after prior refractive surgery. They enrolled patients in the first USA clinical trials, which began in 2008, and the results of those studies led to the FDA determination that cross-linking is a safe and effective treatment.

Corneal cross-linking involves administering riboflavin (vitamin B2) eye drops and UVA light in carefully selected parameters that strengthen the front layers of the cornea (clear covering of the eye) and avoid damage to the back part of the eye.

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 Food and Drug Administration (for use with KXL System in corneal CXL for the treatment of progressive keratoconus.

Currently, the only CXL treatment approved by the 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.

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 Food and Drug Administration for use with KXL System in corneal CXL for the treatment of progressive keratoconus.

PRIOR APPROVAL

Not applicable.

POLICY

Progressive Keratoconus

Epithelium-off corneal collagen cross linking using riboflavin (Photrexa®) and ultraviolet A procedure may be considered **medically necessary** as a **one-time treatment** in the effected eye(s) when the following requirements have been met.

- The individual is ≥ 14 years old; **and**
- The individual has been diagnosed with progressive keratoconus; **and**

Documentation supports a progressive keratoconus/corneal ectasia with **one or more of the following measurements**:

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

The individual has progressive deterioration in vision which has not responded to standard conservative treatment (e.g., spectacles, contact lenses).

Corneal Ectasia

Note: Refer to the individual's benefit document to determine coverage related to refractory surgery, if benefits are available the below criteria will be applicable.

Epithelium-off corneal collagen cross linking using riboflavin (Photrexa®) and ultraviolet A procedure may be considered **medically necessary** as a **one-time treatment** in the effected eye(s) when the following requirements have been met.

- The individual's *contract considers refractive surgery a covered service*; **and**
- The individual is ≥ 14 years old; **and**

- The individual has been diagnosed with corneal ectasia resulting from refractive surgery; **and**

Documentation supports a progressive keratoconus/corneal ectasia with **one or more of the following measurements**:

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

The individual has progressive deterioration in vision which has not responded to standard conservative treatment (e.g., spectacles, contact lenses).

Refer to the individual's benefit document to determine coverage. Wellmark Blue Cross and Blue Shield (BCBS) does not consider surgery and services to diagnose or correct a refractive error, including intraocular lenses and laser vision correction surgery (e.g., LASIK surgery, asigmatic keratotomy, & radial keratotomy) to be a covered benefit, therefore, corneal ectasia resulting from refractive surgery is **not a covered benefit.**

Investigational Statements

Epithelial on corneal collagen cross-linking (CXL) is considered **investigational**.

Corneal collagen cross-linking is considered **investigational** for any other indication not meeting the above criteria to include individuals less than 14 years of age.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0402T Collagen cross-linking of cornea, including removal of the corneal epithelium, when performed, and intraoperative pachymetry, when performed
- J2787 Riboflavin 5'-phosphate, ophthalmic solution, up to 3 ml

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POLICY HISTORY

Date	Reason	Action
September 2021	Annual Review	Policy Revised
September 2020	Annual Review	Policy Revised
September 2019	Annual Review	Policy Revised
September 2018	Annual Review	Policy Revised
September 2017	Annual Review	Policy Renewed
September 2016		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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