Title: Corneal Collagen Cross-Linking

Related Policies:
- Corneal Topography/Computer-Assisted Corneal Topography/Photokeratoscopy

**Professional**
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**DESCRIPTION**

Corneal collagen cross-linking (CXL) is a photochemical procedure approved by the U.S. Food and Drug Administration (FDA) for the treatment of progressive keratoconus and corneal ectasia. Keratoconus is a dystrophy of the cornea characterized by progressive deformation (steepening) of the cornea while corneal ectasia is keratoconus that occurs after refractive surgery. Both lead to functional loss of vision and need for corneal transplantation.

**OBJECTIVE**

The objective of this evidence review is to assess whether the use of epithelium-off corneal collagen cross-linking using riboflavin and ultraviolet A improves the net health outcome for treatment of patients with progressive keratoconus and corneal ectasia after refractive surgery.

**BACKGROUND**

**Keratoconus and Ectasia**

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 laser in situ keratomileuses, although generally, results of these techniques have been poor. Implantation of intrastromal corneal ring segments (see evidence review 9.03.14) 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, penetrating keratoplasty is required.

None of the currently available treatment options for keratoconus and corneal ectasia halt the progression of the disease, and corneal transplantation is the only option available when functional vision can no longer be achieved.

Corneal collagen cross-linking has the potential to slow the progression of the disease. It is performed with the photosensitizer riboflavin (vitamin B2) and ultraviolet A irradiation. There are 2 protocols for corneal collagen cross-linking:

1. **Epithelium-off corneal collagen cross-linking** (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 ultraviolet A 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-mm thick stroma (endothelium, anterior chamber, iris, lens, retina) are not exposed to an ultraviolet dose that is above the cytotoxic threshold.
2. Epithelium-on corneal collagen cross-linking (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 corneal collagen cross-linking treatment approved by the U.S. Food and Drug Administration (FDA) is the epithelium-off method. There are no FDA approved corneal collagen cross-linking treatments using the epithelium-on method. Corneal collagen cross-linking is being evaluated primarily for corneal stabilization in patients with progressive corneal thinning, such as keratoconus and corneal ectasia following refractive surgery. Corneal collagen cross-linking may also have anti-edematous and antimicrobial properties.

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 FDA for use with KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia after refractive surgery.¹
POLICY

A. Corneal collagen cross-linking using riboflavin and ultraviolet A may be considered **medically necessary** as a treatment of progressive keratoconus or corneal ectasia resulting from refractive surgery in patients who have failed conservative treatment (e.g., spectacle correction, rigid contact lens) (see Policy Guidelines).

B. Corneal collagen cross-linking using riboflavin and ultraviolet A is considered **experimental / investigational** for all other indications.

Policy Guidelines

1. Progressive keratoconus or corneal ectasia is defined as 1 or more of the following:
   a. An increase of 1 diopter (D) in the steepest keratometry value
   b. An increase of 1 D in regular astigmatism evaluated by subjective manifest refraction
   c. A myopic shift (spherical equivalent) of 0.50 D on subjective manifest refraction
   d. A decrease ≥0.1 mm in the back optical zone radius in rigid contact lens wearers where other information was not available.

2. Some contracts do not cover refractive surgery. When refractive surgery is not covered, any service or supply provided or obtained relative to an excluded service is considered a general exclusion based on member contract.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through February 9, 2021.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.
CORNEAL COLLAGEN CROSS-LINKING FOR KERATOCONUS

Clinical Context and Therapy Purpose
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.2,3 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 diopters (D) in First Definite Apical Clearance Lens (a rigid contact lens to measure corneal curvature) and 1.6 D in flatter keratometric reading.

The purpose of corneal collagen cross-linking using riboflavin and ultraviolet A irradiation in patients with keratoconus is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does corneal collagen cross-linking using riboflavin and ultraviolet A in patients with keratoconus improve net health outcomes?

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

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

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 are actively managed by an ophthalmologist.

Comparators
The comparators of interest are observation, rigid or specialty contact lens, intracorneal ring segments, or corneal transplant.

Patients with progressive keratoconus 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. Negative outcomes include infection, adverse reactions, and need for alternative treatment, including corneal transplant.

Follow-up of at least 1 year is needed to assess outcomes.
Visual acuity definitions
Best spectacle-corrected visual acuity is the best vision correction that can be achieved with glasses as measured on the standard Snellen eye chart.

Best corrected visual acuity is the best vision correction that can be achieved with any visual correction (e.g. glasses, contact lenses, keratonomy) as measured on the standard Snellen eye chart.

Uncorrected visual acuity is the vision correction without visual correction as measured on the standard Snellen eye chart.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

The evidence base for U.S. Food and Drug Administration (FDA) approval of epi-off corneal collagen cross-linking (PHOTREXA VISCOS, PHOTREXA, and KXL System; Avedro, Inc.) 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.

Review of Evidence

Pivotal Trials for Epi-Off Corneal Collagen Cross-Linking for Keratoconus
Three open-label RCTs informed the FDA’s approval. They were named Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes With Corneal Ectasia or Progressive Keratoconus (UVX-001 Keratoconus and UVX-001 Ectasia) (a combined trial), Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes With Progressive Keratoconus (UVX-002) for keratoconus, and Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes With Corneal Ectasia After Refractive Surgery (UVX-003) for ectasia. All 3 trials followed the same protocol. The primary endpoint was originally a 1-D reduction in the maximum corneal curvature at month 3. Because corneal stromal remodeling associated with healing response after corneal collagen cross-linking requires 6 to 12 months to stabilize, the time point for the primary endpoint was changed from 3 to 12 months. This endpoint was better suited for evaluating the long-term clinical benefits of the corneal collagen cross-linking treatment. In all 3 trials, only 1 eye per patient was designated as the experimental eye. Patients with corneal ectasia diagnosed after laser in situ keratomileusis or photorefractive keratectomy or those with progressive keratoconus were included in these trials.

The following discussion and tables will focus on UVX-001 Keratoconus and UVX-002’s results. UVX-001 (Table 1; Table 2). Ectasia and UVX-003, as well as pooled results of UVX-001, will be covered in the second indication on ectasia.
Progressive keratoconus was defined as one or more of the following over a period of 24 months or less before randomization:

- An increase of 1D 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 ultraviolet A light source turned on. For sham subjects who received corneal collagen cross-linking treatment at months 3 or 6, the last maximum corneal curvature measurement recorded before corneal collagen cross-linking 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 corneal collagen cross-linking treatment at months 3 or 6, and therefore the analysis compared the maximum corneal curvature at month 12 in the corneal collagen cross-linking group with the maximum corneal curvature at months 3 or 6 in the sham group. In each study, maximum corneal curvature was assessed at baseline and months 1, 3, and 12. By months 6 and 12, the corneal collagen cross-linking group saw greater reduction in corneal curvature than the sham group. Table 1 summarizes the maximum corneal curvature results for UVX-001 Keratoconus and UVX-002.

### Table 1. Mean (SD) Diopter Change From Baseline Kmax for Progressive Keratoconus

<table>
<thead>
<tr>
<th>Study</th>
<th>UVX-001 Keratoconus</th>
<th>UVX-002</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (n=29)</td>
<td>CXL (n=29)</td>
</tr>
<tr>
<td></td>
<td>62 (8.3)</td>
<td>61 (7.3)</td>
</tr>
<tr>
<td>Baseline</td>
<td>60 (9.2)</td>
<td>61 (9.8)</td>
</tr>
<tr>
<td>Mo 1</td>
<td>-0.8 (2.4)</td>
<td>1.4 (2.7)</td>
</tr>
<tr>
<td></td>
<td>0.3 (2.2)</td>
<td>1.2 (3.4)</td>
</tr>
<tr>
<td>Mo 3</td>
<td>0.1 (2.6)</td>
<td>-0.3 (2.7)</td>
</tr>
<tr>
<td></td>
<td>0.2 (2.4)</td>
<td>-0.6 (4.4)</td>
</tr>
<tr>
<td>Mo 6</td>
<td>0.5 (3.0)</td>
<td>-0.9 (2.6)</td>
</tr>
<tr>
<td></td>
<td>0.6 (2.8)</td>
<td>-1.1 (5.1)</td>
</tr>
<tr>
<td>Mo 12</td>
<td>0.5 (3.0)</td>
<td>-1.4 (2.8)</td>
</tr>
<tr>
<td></td>
<td>0.6 (2.8)</td>
<td>-1.7 (4.7)</td>
</tr>
</tbody>
</table>

Adapted from Center for Drug Evaluation and Research.4, CI: confidence interval; CXL: corneal collagen cross-linking; Kmax: maximum corneal curvature; NA: not applicable; SD: standard deviation;

### Best Spectacle-Corrected Visual Acuity

The pivotal trials also assessed visual acuity outcomes by mean improvement in best spectacle-corrected visual acuity.4 A gain of ≥ 15 letters on the Early Treatment Diabetic Retinopathy
Study test was considered clinically meaningful. Both trials showed greater improvement for the corneal collagen cross-linking group than for the sham group at 12 months (UVX-001: 7.2 vs. 3.4 letters, p=.1685; UVX-002: 5.0 vs. 1.4 letters, p=.0280). For UVX-001, the proportion of participants with a ≥15-letter improvement in Best spectacle-corrected visual acuity was comparable between groups at 12 months (based on last observation carried forward). Statistical procedures to control for type I error for multiple comparisons were not described in FDA documents. Therefore, these results should not be used for statistical inference. 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 with +5.8 (n=96) for corneal collagen cross-linking treated patients, yielding a difference of 4.7 letters in favor of corneal collagen cross-linking 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 corneal collagen cross-linking treatment. Notably, FDA-approved labels for Photrexa and Photrexa Viscous do not include any visual acuity outcomes. Table 2 summarizes the 1-year results of UVX-002 compared to baseline.

**Table 2. UVX-002 1-Year Results Compared to Baseline**

<table>
<thead>
<tr>
<th>Measurement Points</th>
<th>UDVA^a</th>
<th>CDVA^a</th>
<th>MRSE^b</th>
<th>Manifest Astigmatism^b</th>
<th>Kmax^b</th>
<th>Average K^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratoconus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-op (SD)</td>
<td>0.87 (0.35)</td>
<td>0.39 (0.27)</td>
<td>-9.32 (5.65)</td>
<td>5.09 (2.54)</td>
<td>60.4 (9.99)</td>
<td>50.4 (7.06)</td>
</tr>
<tr>
<td>1 y (SD)</td>
<td>0.82 (0.39)</td>
<td>0.25 (0.23)</td>
<td>-8.47 (5.50)</td>
<td>5.01 (2.43)</td>
<td>58.4 (8.41)</td>
<td>48.9 (5.48)</td>
</tr>
<tr>
<td>P-value</td>
<td>NS</td>
<td>&lt;.001</td>
<td>NS</td>
<td>NS</td>
<td>.002</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Adapted from Hersh et al (2011).^5 CDVA: corrected distance visual acuity; K: keratometry value; Kmax: maximum corneal curvature; MRSE: manifest refraction spherical equivalent; NS: not statistically significant (p-value not reported); pre-op: pre-operation; SD: standard deviation; UDVA: uncorrected distance visual acuity;

**Other Randomized Controlled Trials**

Hersh et al (2017) analyzed 205 patients who had keratoconus treated with corneal collagen cross-linking (n=102) or a sham procedure (n=103) in a phase 3, prospective, randomized, controlled trial. At 1 year, those in the treatment group had a significant decrease in maximum corneal curvature score (1.6) compared with baseline, while the control group saw an increase in maximum corneal curvature (1.0); the between-group difference in maximum corneal curvature change was 2.6 D (p<0.001). Mean corrected distance visual acuity improved significantly more in the treatment group (5.7 Logarithm of the Minimum Angle of Resolution - logMAR) than in the control group (2.2 logMAR; between-group difference, 3.5 logMAR; p<0.01). A similar finding, though statistically insignificant, was observed for mean uncorrected distance visual acuity, with the treatment group improving by 4.4 logMAR, compared with the
control group (2.6 logMAR; between-group difference, 1.8 logMAR). Endothelial cell count did not change significantly from baseline to 1 year in either group. The trial was limited in that patients in the control group were allowed to switch to corneal collagen cross-linking treatment after 3 months; thus, their data were imputed based on the last observation carried forward method. Also, in the control group, patients did not undergo removal of their epithelium.

Renesto et al (2010) reported on 2-year results of a randomized trial that compared corneal collagen cross-linking with 1 month of riboflavin eye drops in 39 eyes of 31 patients with keratoconus. After 3 months, all patients received intrastromal corneal ring segments (see evidence review 9.03.14). Patients were evaluated at 1 and 3 months after treatment with corneal collagen cross-linking or riboflavin, and then at 1, 3, 6, 12, and 24 months after intrastromal corneal ring segments insertion. There were no significant differences between the 2 groups for uncorrected visual acuity, best-corrected visual acuity, or in 3 topographic parameters (flattest K, steepest K, and average keratometry) throughout the 24-month follow-up.

Systematic Reviews

A Cochrane review (2015) 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 of 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.

Meri et al (2016) 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.

McAnena et al (2017) 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).
Nonrandomized Studies

Longer-term follow-up has been reported from Europe, where corneal collagen cross-linking has been performed for a greater number of years. Indications for treatment typically include progression of steepening (increase in maximum corneal curvature 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.

Toprak et al (2017) retrospectively analyzed 29 eyes from pediatric patients (age range, 10-17 years) whose progressive keratoconus was treated with unilateral corneal collagen cross-linking treatment.\(^\text{11}\) From baseline to 2-year follow-up, there was a significant decrease in mean corrected distance visual acuity (0.34 logMAR to 0.13 logMAR; \(p<0.001\)). Maximum keratometry measures decreased from baseline 54.65 to 53.25 at 2 years (\(p=0.034\)), while anterior chamber parameters, corneal thickness, and corneal volume were not significantly affected by corneal collagen cross-linking after 2 years (\(p>0.05\)). Several parameters of the Scheimpflug imaging system were improved following corneal collagen cross-linking treatment: index of surface variance decreased from 69.75 at baseline to 62.95 at 2 years (\(p=0.004\)); keratoconus index decreased from 1.16 to 1.14 (\(p=0.001\)); center keratoconus index decreased from 1.05 to 1.04 (\(p=0.004\)); and index of height decentration decreased from 0.056 to 0.042 (\(p=0.001\)). The radius of minimum curvature increased significantly from baseline to 2 years (6.21 to 6.36; \(p=0.007\)), although 2 other indices (indices of height and vertical asymmetry) did not change significantly. The authors noted that follow-up beyond 2 years is required to make long-term assessments of corneal collagen cross-linking as a treatment for keratoconus, but concluded that their results seemed favorable for postoperative outcomes.

Badawi et al (2017) published a prospective nonrandomized observational study of accelerated corneal collagen cross-linking to treat pediatric patients with keratoconus.\(^\text{12}\) Of the 25 patients (33 eyes) enrolled, 80% were male, and most patients (n=17) received unilateral corneal collagen cross-linking, administered with VibeX Rapid solution and Vega CBM X-Linker. The group’s mean unaided and aided visual acuity were significantly improved at all time points (3, 6, and 12 months). At 12-month follow-up, the mean unaided visual acuity score was 0.34, which was a significant decrease compared with preoperative mean score (0.54; \(p<0.001\)). For aided visual acuity, there was a similar decrease from preoperative (0.36) to 12-month (0.17) time points (\(p<0.001\)). Mean corneal astigmatism values also decreased significantly (preoperative 2.4 D decreased to 2.01 D at 12 months; \(p<0.001\)). The mean maximum corneal curvature showed an average flattening of 1.2 D in 1 year (49.12 D decreasing to 47.9 D; \(p<0.001\)); the authors reported significant improvements in other measures such as central pachymetry, maximum anterior elevation, average progression indices, and Q values. A limitation of the study was the slight increase observed in posterior surface elevation, which, contrary to other study measures, showed no significant positive effect 12 months after accelerated corneal collagen cross-linking (\(p=0.9\)). Advising further study of the procedure, the authors noted that the unusual result might be accounted for by the choice of Pentacam as a corneal analysis tool because there might have been corneal artifacts present during evaluation.

Knutsson et al (2018) 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.\(^\text{13}\) 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 2 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.

Papaioannou et al (2016) retrospectively analyzed 377 eyes of 336 patients (mean age, 15 years) who underwent corneal collagen cross-linking for progressive keratoconus. There was a significant improvement in mean Best spectacle-corrected visual acuity from 0.33 to 0.27 logMAR (p<0.05). The authors found that the benefits of corneal collagen cross-linking in stabilizing keratoconus were maintained for more than 2 years in most pediatric eyes. Padmanabhan et al (2017) published follow-up results from the retrospective study previously mentioned of 377 eyes in 336 pediatric patients. Of 59 eyes for which investigators had longer-term follow-up data (4 to 6.7 years), 30.9% showed worsening corrected distance visual acuity, and 24% showed corneal steepening of greater than 1 D (maximum corneal curvature). These results showed the majority of patients still experienced improvements or stabilization of keratoconus-related outcomes after corneal collagen cross-linking, but suggested that long-term there may be less efficacy.

Raiskup-Wolf et al (2008) reported on outcomes of 241 eyes (272 patients) treated with corneal collagen cross-linking, 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 (maximum corneal curvature) improved or remained stable in 86% of eyes, and best-corrected visual acuity improved by at least 1 line in 53% of the eyes. Three years after treatment (n=33), maximum corneal curvature improved by a mean of 2.57 D in 67% of eyes while best-corrected visual acuity improved by at least 1 line in 58% of eyes. In 2015, the same group published a 10-year follow-up of corneal collagen cross-linking 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 corneal collagen cross-linking, 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 were limited by their retrospective designs and the small number of cases with extended follow-up.

A publication from the Siena Eye Cross Study (2010) reported on 52-month mean follow-up (range, 48-60 months) for 44 keratoconic eyes treated with corneal collagen cross-linking.
Follow-up evaluations were performed at 1, 2, 3, 6, 12, 24, 36, 48, and 60 months after corneal collagen cross-linking. 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, uncorrected visual acuity 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 events included stromal edema in the first 30 days (70% of patients) and temporary haze (9.8% of patients). No persistent adverse events were observed.

Section Summary: Corneal Collagen Cross-Linking for Keratoconus
The evidence for corneal collagen cross-linking for keratoconus includes 2 pivotal trials, other RCTs, systematic reviews, and numerous nonrandomized studies. 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 2 years.

CORNEAL COLLAGEN CROSS-LINKING FOR ECTASIA

Clinical Context and Therapy Purpose
Ectasia (also known as keratectasia, iatrogenic keratoconus, or secondary keratoconus) is a serious long-term complication of laser in situ keratomileusis 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.

The purpose of corneal collagen cross-linking using riboflavin and ultraviolet A irradiation in patients with ectasia is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does corneal collagen cross-linking using riboflavin and ultraviolet A in patients with corneal ectasia improve net health outcomes?

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

Populations
The relevant population of interest is patients with corneal 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 corneal 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.

Patients with corneal ectasia are actively managed by an ophthalmologist. Corneal transplant is performed by an ophthalmologist or ophthalmologic surgeon in an outpatient surgical setting.

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. Negative outcomes include infection, adverse reactions, and need for alternative treatment, including corneal transplant.

Follow-up of at least 1 year is needed to assess outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Pivotal Trials for Epi-Off Corneal Collagen Cross-Linking for Ectasia
As discussed in indication 1, three open-label RCTs informed the FDA’s approval of corneal collagen cross-linking. This section focuses on the UVX-001 Ectasia and UVX-003 studies, which also assessed corneal collagen cross-linking for ectasia. Study protocols were the same for all studies and are explained in more detail in the first indication. Change in maximum corneal curvature was a primary outcome; Table 3 summarizes 1-year change in maximum corneal curvature for corneal ectasia.

Table 3. Mean (SD) Diopter Change from Baseline Kmax for Corneal Ectasia

<table>
<thead>
<tr>
<th>Study</th>
<th>UVX-001 Ectasia</th>
<th>UVX-003</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (n=25)</td>
<td>CXL (n=24)</td>
</tr>
<tr>
<td>Baseline</td>
<td>55 (5.5)</td>
<td>56 (6.3)</td>
</tr>
<tr>
<td>Mo 1</td>
<td>0.8 (1.7)</td>
<td>1.1 (2.1)</td>
</tr>
<tr>
<td>Mo 3</td>
<td>1.0 (1.7)</td>
<td>0.1 (1.3)</td>
</tr>
<tr>
<td>Mo 6</td>
<td>1.0 (1.7)</td>
<td>-0.6 (1.6)</td>
</tr>
</tbody>
</table>
Study | UVX-001 Ectasia | UVX-003
---|---|---
Mo 12 | 1.0 (1.7) | -2.0 (-3.0 to -1.1) | 0.5 (2.3) | -0.5 (2.2) | -1.1 (-1.9 to -0.3)

Adapted from Center for Drug Evaluation and Research.4, CI: confidence interval; CXL: corneal collagen cross-linking; Kmax: maximum corneal curvature; NA: not applicable; SD: standard deviation; UVX-001 Ectasia: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes With Corneal Ectasia or Progressive Keratoconus; UVX-003: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes With Corneal Ectasia After Refractive Surgery.

**Best Spectacle-Corrected Visual Acuity**

The pivotal trials also assessed visual acuity outcomes by mean improvement in Best spectacle-corrected visual acuity.4 Both trials showed greater improvement for the corneal collagen cross-linking group than for the sham group at 12 months (UVX-001: 5.0 vs. -0.9 letters, p=.0184; UVX-003: 5.0 vs. -0.1 letters, p=.0014). For UVX-001, the proportion of participants with a \(\geq 15\) letter improvement in Best spectacle-corrected visual acuity was 33.3% for corneal collagen cross-linking and 8.3% for sham treatment.

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 with +5.8 (n=96) for corneal collagen cross-linking treated patients, yielding a difference of 4.7 letters in favor of corneal collagen cross-linking 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 corneal collagen cross-linking treatment.

Hersh et al (2011) reported on more 1-year results of UVX-002 (keratoconus) and UVX-003 (ectasia). (UVX-002 results are described in the first indication.) The primary outcomes were the same as discussed in the first indication. Table 4 compares the baseline and 12-month results for these outcomes, as well as the pooled results for ectasia and keratoconus combined.

**Table 4. UVX-003 1-Year Results Compared to Baseline**

<table>
<thead>
<tr>
<th>Measurement Points</th>
<th>UDVA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CDVA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MRSE&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Manifest Astigmatism&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Kmax&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Average K&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Ectasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-op (SD)</td>
<td>0.75 (0.30)</td>
<td>0.26 (0.16)</td>
<td>-7.08 (4.10)</td>
<td>4.05 (2.36)</td>
<td>54.7 (7.52)</td>
<td>43.4 (3.54)</td>
</tr>
<tr>
<td>1 y (SD)</td>
<td>0.65 (0.31)</td>
<td>0.19 (0.14)</td>
<td>-.622 (4.93)</td>
<td>4.39 (2.69)</td>
<td>53.7 (6.86)</td>
<td>43.1 (3.09)</td>
</tr>
<tr>
<td>P-value</td>
<td>NS</td>
<td>.02</td>
<td>NS</td>
<td>NS</td>
<td>.08</td>
<td>NS</td>
</tr>
<tr>
<td>All Eyes&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-op (SD)</td>
<td>0.84 (0.34)</td>
<td>0.35 (0.24)</td>
<td>-8.63 (5.30)</td>
<td>4.76 (2.52)</td>
<td>58.6 (9.62)</td>
<td>48.2 (6.97)</td>
</tr>
<tr>
<td>1 y (SD)</td>
<td>0.77 (0.37)</td>
<td>0.23 (0.21)</td>
<td>-7.77 (5.40)</td>
<td>4.81 (2.51)</td>
<td>56.9 (8.62)</td>
<td>47.1 (5.56)</td>
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<tr>
<td>P-value</td>
<td>.04</td>
<td>&lt;.001</td>
<td>.07</td>
<td>.84</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
CDVA: corrected distance visual acuity; K: keratometry value; Kmax: maximum corneal curvature; MRSE: manifest refraction spherical equivalent; NS: not statistically significant (p-value not reported); pre-op: pre-operation; SD: standard deviation; UDVA: uncorrected distance visual acuity; UVX-003: Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes With Corneal Ectasia After Refractive Surgery.

Other Randomized Trials

Hersh et al (2017) compared topographical with visual outcomes of 179 patients treated for corneal ectasia following laser in situ keratomileusis or photorefractive keratectomy surgery.19 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 post-surgery corneal collagen cross-linking were precluded.

Wittig-Silva et al (2008) reported the first RCT of corneal collagen cross-linking.20 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.
Section Summary: Corneal Collagen Cross-Linking for Ectasia
Evidence for corneal collagen cross-linking for corneal ectasia includes 2 pivotal trials and 2 other RCTs. 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.

Adverse Events
For the purposes of this evidence review, adverse events associated with corneal collagen cross-linking are discussed for keratoconus and ectasia together.

The safety analysis conducted by the FDA included 512 eyes (293 eyes with keratoconus, 219 eyes with corneal ectasia) in 364 patients who received corneal collagen cross-linking 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 events resolved in the first month, while others took up to 12 months to resolve. However, in 1% to 6% of patients, these adverse events could continue beyond 12 months.

Summary of Evidence
For individuals who have progressive keratoconus who receive corneal collagen cross-linking using riboflavin and ultraviolet A, the evidence includes multiple randomized controlled trials (RCTs), systematic reviews, and nonrandomized studies. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. In both pivotal RCTs, the primary endpoint (an intermediate outcome) of reducing maximum corneal curvature by 1 diopter (D) was achieved at month 3 and maintained at months 6 and 12 in corneal collagen cross-linking treated patients compared with sham controls. In both RCTs, the difference in mean change in maximum corneal curvature from baseline to 12 months was 1.9 D and 2.3 D, respectively, favoring the corneal collagen cross-linking treated patients. Several other 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.

For individuals who have corneal ectasia after refractive surgery who receive corneal collagen cross-linking using riboflavin and ultraviolet A, the evidence includes multiple RCTs and nonrandomized studies. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. In both pivotal RCTs, the primary endpoint (an intermediate outcome) of reducing maximum corneal curvature by 1 D was achieved at month 3 and maintained at months 6 and 12 in the corneal collagen cross-linking treated patients compared with sham controls. In both RCTs, the difference in mean change in maximum corneal curvature from baseline to 12 months was 2.0 D and 1.1 D, respectively, favoring corneal
collagen cross-linking treated patients. Other 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 3 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.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty society and 1 academic medical center (2 reviewers) while this policy was under review in 2012. The input was mixed, noting the limited literature and lack of U.S. Food and Drug Administration (FDA) approval for this procedure, although there are ongoing clinical trials regulated by the FDA. Reviewers also commented on the lack of alternatives to slow disease progression, and that data indicated the procedure is safe and effective enough to offer to patients with adequate informed consent under an investigational protocol.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Institute for Health and Care Excellence
In 2013, the National Institute for Health and Care Excellence (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. The 2013 guidance stratified recommendations for corneal collagen cross-linking as follows:

“Most of the published evidence on photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A (UVA) for keratoconus and keratococcus relates to the technique known as ‘epithelium-off corneal collagen cross-linking’. ‘Epithelium-on (transepithelial) corneal collagen cross-linking’ is a more recent technique and less evidence is available on its safety and efficacy. Either procedure (epithelium-off or epithelium-on corneal collagen cross-linking) can be combined with other interventions, and the evidence base for these combination procedures (known as ‘corneal collagen cross-linking 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 corneal collagen cross-linking 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) corneal collagen cross-linking, and the combination (corneal collagen cross-linking plus) procedures for keratoconus and keratectasia is inadequate in quantity and quality. Therefore, these procedures should only be used with special arrangements for clinical governance, consent and audit or research.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5. 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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<tr>
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<tr>
<td>NCT01708538a</td>
<td>Phase III Study of Corneal Collagen Cross-linking Using Two Different Techniques</td>
<td>30</td>
<td>Oct 2020</td>
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<tr>
<td>NCT03531047</td>
<td>A Prospective, Controlled Study of Refractive Corneal Cross-linking for Progressive Keratoconus</td>
<td>52</td>
<td>Nov 2021</td>
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<tr>
<td>NCT01112072</td>
<td>Randomized Study of Safety and Efficacy of Corneal Collagen Crosslinking and Intacs for Treatment of Keratoconus and Corneal Ectasia</td>
<td>160</td>
<td>Dec 2021</td>
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<td>NCT03319082a</td>
<td>A Phase IV Observational Registry to Assess the Durability of Effect of Corneal Collagen Cross-linking With Photrexa Viscous, Photrexa, and the KXL System in Patients With Corneal Ectasia Following Refractive Surgery</td>
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<tr>
<td>NCT03760432</td>
<td>Clinical Trial of Laser Custom Corneal Collagen Cross-Linking in Keratoconus</td>
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<td>NCT00560651</td>
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<td><strong>Unpublished</strong></td>
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<td>NCT01604135</td>
<td>Collagen Crosslinking for Keratoconus - a Randomized Controlled Clinical Trial</td>
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<td>NCT01459679</td>
<td>A Multi-Center, Randomized, Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus or Corneal Ectasia After Refractive Surgery</td>
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<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>92</td>
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<tr>
<td>NCT01189864a</td>
<td>Collagen Crosslinking With Ultraviolet-A in Asymmetric Corneas</td>
<td>500</td>
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<td>NCT02721628</td>
<td>Femtosecond Laser Assisted Epikeratoplasty Versus Collagen Cross-Linking in Progressive Keratoconus</td>
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<td>Mar 2018 (unknown; updated 03/29/16)</td>
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NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.
b Terminated to initiate FDA and IND-cleared study protocol.

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**CPT/HCPCS**

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<td>Riboflavin 5’-phosphate, ophthalmic solution, up to 3 mL</td>
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**ICD-10 Diagnoses**

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<tr>
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</tr>
<tr>
<td>H18.603</td>
<td>Keratoconus, unspecified, bilateral</td>
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H18.621 Keratoconus, unstable, right eye
H18.622 Keratoconus, unstable, left eye
H18.623 Keratoconus, unstable, bilateral
H18.711 Corneal ectasia, right eye
H18.712 Corneal ectasia, left eye
H18.713 Corneal ectasia, bilateral

REVISIONS

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<td>Updated Rationale section.</td>
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<tr>
<td>08-01-2018</td>
<td>In Policy section:</td>
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<td>• Revised Policy Guidelines Item 1 c, removed &quot;decrease in the&quot; to read, &quot;A myopic shift (spherical equivalent) of 0.50 D on subjective manifest refraction.&quot;</td>
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<td>01-01-2019</td>
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<td></td>
<td>• Added new HCPCS code: J2787.</td>
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<td>04-24-2019</td>
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<td>In Policy section:</td>
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<td>• In Item A, removed &quot;after&quot; and added &quot;resulting from&quot; to read, &quot;Corneal collagen cross-linking using riboflavin and ultraviolet A may be considered medically necessary as a treatment of progressive keratoconus or corneal ectasia resulting from refractive surgery in patients who have failed conservative treatment (e.g., spectacle correction, rigid contact lens) (see Policy Guidelines).”</td>
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<td>Updated Rationale section.</td>
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<td>07-01-2019</td>
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<td>• Revised nomenclature to CPT code: 0402T.</td>
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<td>Updated References section.</td>
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REFERENCES


Other References
1. Blue Cross and Blue Shield Ophthalmology / Optometric Liaison Committee, February 2017; May 2018.