# Molina Clinical Policy
# Corneal Collagen Cross-Linking (CXL): Policy No. 328

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**OHIO MEDICAID**: All Ohio Medicad prior authorization requests are reviewed for medical necessity on an individual basis.

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## OVERVIEW

**Keratoconus** is a corneal dystrophy distinguished by localized thinning of the corneal stroma with secondary ectasia. This results in progressive myopia and irregular astigmatism with associated progressive loss of vision and reduced quality of life (Daizong 2018). Keratoconus affects approximately one out of every 2000 people. However, this estimate is based on a study that did not use corneal topography, and new studies suggest a prevalence as high as 1 in 375 individuals in certain populations (Asimellis, 2021).

- Treatment is determined by the severity of the disease. Although spectacles or soft contact lenses may suffice in mild cases, rigid gas permeable and scleral contact lenses are frequently required in advanced disease. Keratoplasty is typically reserved for advanced disease with suboptimal vision and contact lens wear tolerance (Mandathara 2017; Daizong 2018). Initially, hard contact lenses are used to flatten the cornea and help it retain its shape. Penetrating keratoplasty (i.e., corneal graft/transplant) is the next line of treatment as the disease progresses or if the patient is unable to tolerate contact lens therapy.
- Various keratorefractive methods, broadly categorized as subtractive and additive techniques, have been attempted as alternatives. These interventions are intended to mitigate a portion of the problems associated with corneal transplantation. Subtractive methods include LASIK, which has yielded generally poor outcomes. Intracorneal ring segments (Intacs), which are surgically implanted into the corneal stroma to reinforce the corneal cone and flatten the central cornea, is another procedure intended to strengthen the cornea, prevent future deterioration, and obviate the need for a penetrating keratoplasty as an estimated 20% of keratoconus patients will require corneal transplantation (O'Brart, 2014). These therapies aim to reduce refractive errors; however, none alter the course of the disease, and patients with advanced disease frequently require corneal transplantation for visual rehabilitation (Hayes 2022).

**Corneal Ectasia** (also known as keratectasia, iatrogenic keratoconus, or secondary keratoconus) is a long-term disorder characterized by gradual corneal thinning and steepening, resulting in corneal optical abnormalities and loss of visual acuity. Ectasia occurs postoperatively and primarily affects older populations. Almost invariably the cause is refractive eye surgery, most commonly laser in situ keratomileusis (LASIK) surgery and photorefractive keratectomy (PRK). Because the corneal "wall" has been rendered thinner after LASIK, internal pressure from within the eye might cause corneal expansion or distension. In addition to CXL, corneal ectasias can be treated with corrective lenses, gas permeable contact lenses, intraocular lenses, and minimally invasive intracorneal ring segment implantation (e.g., Intacs, Keraring, Ferrara ring, Myoring). Many patients cannot tolerate the rigid lenses and the initial effects of the rings are reported to regress with time. Other options include ablative procedures such as photorefractive keratectomy, phototherapy keratectomy, lamellar keratoplasty, and penetrating keratoplasty; however, none of these treatments change the course of the disease, and patients with advanced disease frequently require corneal transplantation.

Both progressive keratoconus and ectasia lead to functional loss of vision and need for corneal transplantation since none of the currently available treatment options for keratoconus and corneal ectasia halt the progression of the disease. Corneal transplantation is the only option available when functional vision can no longer be achieved.

**CXL is an in-office procedure FDA-approved to treat progressive keratoconus and corneal ectasia to preserve visual function.** CXL reinforces the cornea by preventing or diminishing the gradual thinning and steepening of a cornea weakened by keratoconus, other corneal illness, or corneal ectasia after refractive surgery (Gomes 2015). CXL is a procedure that creates crosslinks in the collagen of the corneal stroma by photosensitizing it with riboflavin (vitamin B2) and exposing it to ultraviolet A (UVA) light, resulting in greater biomechanical rigidity of the corneal stroma (Wollensak 2003a,b; Wollensak & Iomdina 2009). The mechanism of action of CXL treatments is unknown; they may increase the number of 'anchors' that connect collagen fibers and strengthen the cornea (NICE, 2013). While CXL slows the growth of keratoconus by increasing corneal stiffness, it has no effect on functional vision. There are two different methods of cross-linking the collagen in the cornea:

1. **Epithelium-off collagen crosslinking ("epi-off" CXL):** In the epi-off CXL procedure, the epithelium of the cornea is removed to allow the liquid riboflavin to more easily penetrate the corneal tissue. Riboflavin eye drops are applied to the corneal surface before the procedure and intermittently during the procedure. The corneal surface is then exposed to UVA radiation. Postoperatively, topical antibiotics and anti-inflammatory drops are normally prescribed, with topical steroids if necessary. In some cases, a bandage contact lens may also be used for a few days. The procedure is done on one eye at a time and may also be repeated if needed. CXL is generally not performed in patients with active or history of herpes simplex virus keratitis, thin corneas, or corneal hydrops (UpToDate 2020). **Conventional corneal cross-linking (C-CXL) is a procedure and therefore not subject to FDA regulation. However, any medical devices, drugs, or tests used as part of the procedure may be subject to FDA regulation.**

   Photrexa (riboflavin 5-phosphate ophthalmic solution) and Photrexa Viscous (riboflavin 5-phosphate in 20% dextran solution) were approved for use with the KXL UVA Light system for the treatment of progressive keratoconus (April 2016; NDA 203324). Photrexa Viscous and Photrexa are photoenhancers indicated for use with the KXL System in CXL for the treatment of progressive keratoconus, according to the package insert. The original indication was expanded to include "orneal ectasia following refractive surgery" (July 2016).

2. **Epithelium-on CXL ("epi-on" or transepithelial):** The corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed (NICE, 2013). NICE found inadequate evidence of the safety and efficacy of epithelium-on (transepithelial) CXL. **There are no FDA approved CXL treatments using the epithelium-on method of CXL.**

Either procedure (epi-off or epi-on CXL) can be combined with other interventions such as intrastromal corneal ring segments, PRK or phakic intraocular lens implantation to improve visual acuity. The evidence basis for these combination procedures (also known as "CXL-plus") is limited (NICE, 2013).

**Epithelium-off CXL ("epi-off") Treatment**

- CXL with riboflavin 5'-phosphate ophthalmic solution (Photrexa 0.146%; Photrexa Viscous 0.146% in Dextran 20%) and UVA irradiation (KXL System) reduces clinical progression and improves visual acuity in individuals with progressive keratoconus or post-refractive surgery corneal ectasia. However, it is uncertain to what extent it will allow patients to avoid corneal transplantation. RCTs show that corneal CXL lowers and in some cases reverses corneal steepening that reduces visual acuity in the short term, but the long-term effects are unclear.
- Disease status, functional results, and treatment-related morbidity are relevant outcomes. RCTs, including several pivotal trials, suggest short-term improvements in corneal steepening and visual acuity with CXL. Results from one trial have reported that these benefits are maintained at two to three years.
- Some retrospective studies have indicated positive 10-year outcomes, however these findings had small sample sizes at long-term follow-up and limited information on all patients treated with corneal CXL within the same time period. Long-term results may be seen in prospective trials involving large numbers of participants. Longer-term outcomes from large cohorts will also be useful to evaluate potential long-term complications of this new treatment approach.
- Further research is required to determine whether corneal CXL improves long-term outcomes and to evaluate other crucial factors, such as: defining the inclusion and exclusion criteria for progression of disease, types and number of prior refractive procedures (including non-laser based refractive procedures), the optimal time between prior refractive treatment and CXL for affected eyes, and outcomes based on the original corneal thickness versus the corneal thickness after treatment (CDER, NDA 203324).

## COVERAGE POLICY

Epithelium-off CXL using riboflavin and ultraviolet A for the treatment of progressive keratoconus or corneal ectasia resulting from refractive surgery **may be considered medically necessary** when **ALL** of the following clinical criteria are met:

1. Diagnosis of **ONE** of the following supported by clinical documentation:
   a. Progressive keratoconus (thinning of the cornea); **OR**
   b. Corneal ectasia (corneal thinning and protrusion) after refractive surgery (e.g., LASIK or PRK)

   **NOTE:** In keratoconus and ectatic disease, diagnostic metrics include corneal topography, corneal pachymetry, corneal epithelial thickness, posterior corneal topography, wavefront analysis, and corneal biomechanics. Documentation may include any of the listed diagnostic metrics.

**AND**

2. Member meets **ONE** of the following **(A OR B)** according to specific diagnosis:

   A. **Progressive Keratoconus**
      1. At least **ONE** of the following changes have occurred within the 24 months:
         a. Increase of 1.00 diopters (D) or more in the steepest keratometry measurement; **OR**
         b. Increase of 1.00 D or more in manifest cylinder; **OR**
         c. Increase of 0.50 D or more in manifest refraction spherical equivalent (MRSE)

      **AND**
      2. Corrected distance visual acuity worse than 20/20 with properly fitted spectacles or contact lenses

      **AND**
      3. Corneal thickness 300 microns or more

   **OR**

   B. **Corneal ectasia resulting from refractive surgery (e.g., LASIK)**
      1. Corrected distance visual acuity worse than 20/20

      **AND**
      2. Corneal thickness of at least 300 microns at the thinnest area

**AND**

3. Requested treatment for ONE of the following. Documentation required:
   a. Left eye; **OR**
   b. Right eye

**AND**

4. Documentation within medical record that member does not have ANY of the following:
   a. Absence of visual disturbance from a significant central corneal opacity or other eye disease (e.g., herpetic keratitis, neurotrophic keratopathy); **AND**
   b. No history of corneal or systemic disease that would interfere with healing after the procedure such as chemical injury or delayed epithelial healing in the past

### CONTINUATION OF THERAPY

Repeat treatment in the same eye is not supported by compendia and not considered not medically necessary.

### LIMITATIONS AND EXCLUSIONS

The following are considered **contraindications/exclusions/discontinuations** based on insufficient evidence:[AAO, 2017b]

1. Corneal thickness of < 300 microns
2. Prior herpetic infection (due to possible viral reactivation)
3. Concurrent infection

4. Severe corneal scarring or opacification
5. History of corneal surgery, including intracorneal ring segments
6. History of poor epithelial wound healing; or History of corneal disease that would interfere with healing after the procedure, such as chemical injury or delayed epithelial healing in the past
7. Severe ocular surface disease (e.g., dry eye)
8. Autoimmune disorders

The following are considered **experimental, investigational and unproven** based on insufficient evidence:

1. Any indications other than those listed above
   **NOTE:** CXL is considered experimental, investigational or unproven for any other indication including when combined with a second refractive procedure. Any other type of collagen cross-linking procedures (e.g., epithelium-on/trans-epithelial) is considered experimental, investigational or unproven for any indication, including but not limited to treatment of infectious keratitis and in combination with other procedures (e.g., intrastromal corneal ring segments, PRK or phakic intra-ocular lens implantation) (CXL-plus).
2. Repeat treatment in the same eye is not supported by compendia and not considered not medically necessary.

**PRESCRIBER REQUIREMENTS:** Prescribed by board-certified ophthalmologist or cornea specialist who specializes in the surgical treatment of keratoconus; **AND**

Requested procedure and appropriate follow-up will be carried out by ophthalmologist with expertise in managing corneal disease and specific training in the use of UV light or by appropriately trained staff under their supervision

**AGE RESTRICTIONS:** 14 years of age or older
*Safety and efficacy not established in pediatric patients 14 years of age and younger (Photrexa, 2019)*

**DOCUMENTATION REQUIREMENTS.** Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

## DRUG INFORMATION

**ROUTE OF ADMINISTRATION:** Photrexa-Photrexa Viscous Kit: Photrexa 0.146%; Photrexa Viscous 0.146% in Dextran 20% (6 mL) [contains dextran]. Photrexa is administered during the CXL procedure.

**DRUG CLASS:** Corneal Collagen Cross-Linking Agent, Ophthalmic; Ophthalmic Agent

**FDA-APPROVED USES**
Photrexa (riboflavin 5'-phosphate ophthalmic solution) 0.146% and Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) is indicated for the treatment of:

- **Keratoconus, progressive:** Treatment of progressive keratoconus with the KXL System in corneal collagen cross-linking
  The FDA issued a new drug application (NDA) approval for Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%, and Photrexa (riboflavin 5'phosphate ophthalmic solution) 0.146%, to be used with the KXL System (Avedro, Inc., Waltham, MA), a UV light source, for the treatment of progressive keratoconus (April 2016).
- **Corneal ectasia following refractive surgery:** Treatment of corneal ectasia following refractive surgery with the KXL System in corneal collagen cross-linking (July 2016)
  The FDA supplemented the NDA approval for the treatment of corneal ectasia following refractive surgery. The NDA noted that the safety and effectiveness of corneal collagen crosslinking has not been established in patients age < 14 years and the clinical trials did not include patients who were age 65 years or older (FDA 2016, reviewed 2019).

Refer to the prescribing information for specific dosage and administration instructions which indicates usage only of the conventional epi-off CXL protocol since the KXL® system has not been approved for the use with any other protocol (e.g., transepithelial "epithelium-on") or for other indications (e.g., infectious keratitis, corneal ulcers).

**COMPENDIAL APPROVED OFF-LABELED USES:** None

## SUMMARY OF MEDICAL EVIDENCE

The peer-reviewed medical evidence for CXL in individuals who have keratoconus includes randomized controlled trials (RCTs), prospective trials with historical controls, prospective comparative cohort studies, retrospective comparative cohort studies and systematic reviews. Outcomes reported are change in disease status, functional outcomes, and treatment-related morbidity. Evidence from the available studies suggests that CXL may slow or stop progression of keratoconus relative to no treatment or sham treatment as indicated by altered corneal topography, specifically, flattening of the cornea. Findings were inconsistent for visual acuity and corneal thickness outcomes, and CXL does not seem to impact measures of refraction. CXL appears to be generally safe, with impaired epithelial healing and corneal haze as the most commonly reported complications. The available studies were relatively small, with intermediate-term follow-up (1-3 years); therefore, the long-term efficacy and safety of the procedure are not known.

CXL was first introduced by Wollensak and colleagues (2003) with an UVA protocol with an exposure time of 30 minutes (referred to as the 'Epithelium-off' 'Dresden Protocol'). The procedure uses the photochemical interaction of UVA and riboflavin (vitamin B2), to induce cross-links between corneal stromal macromolecules. CXL has been proven in its effectiveness and safety in halting the progression of keratoconus and improving topographic and visual parameters in numerous prospective, published studies, including RCTs (Wollensak; Hoyer 2009 ; Meiri 2016; McAnena 2017; Padmanabhan 2017).

The evidence base for the FDA approval of epi-off CXL for the treatment of progressive keratoconus and corneal ectasia after refractive surgery consists of 3 prospective, randomized, open-label, and sham-controlled trials (Table 1). In addition, there are systematic reviews, 2 RCTs, and multiple prospective controlled studies as well as uncontrolled trials reporting on longer-term outcomes of the procedure.

FDA approval of Photrexa Viscous and Photrexa was based on 3 prospective RCTs open-label, sham-controlled trials in a total of 384 patients ≥14 years old with progressive keratoconus (Table 1). The studies were titled 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 The identical protocol was used for all 3 trials. Initially, the primary endpoint was a 1-D reduction in maximum corneal curvature at month 3. Because corneal stromal remodeling associated with the healing response following CXL requires 6 to 12 months to stabilize, the primary endpoint was adjusted from 3 to 12 months.

Patients received a single treatment and were followed for 12 months. CXL-treated eyes had significant reductions in corneal curvature at 6 and 12 months compared to sham-treated eyes; these improvements were generally correlated with improvements in best corrected visual acuity (BCVA). This endpoint was more appropriate for assessing the long-term clinical benefits of corneal collagen cross-linking. Only 1 eye per patient was assigned as the experimental eye in each of the 3 trials. These trials included patients with corneal ectasia diagnosed following LASIK or PRK, as well as those with progressive keratoconus.

- Patients with corneal ectasia diagnosed after LASIK or PRK 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.

- Results
  - At 12 months, an average Kmax *reduction* of 1.0 diopter and 0.5 diopter was seen in Photrexa-treated eyes in study 1 and study 3, respectively.
  - In the sham-treated eyes, an average *increase* of 1.0 diopter and 0.5 diopter in study 1 and study 3, respectively, was seen at 12 months.
  - The difference between the Photrexa- and sham-treated groups was -2.0 diopters and -1.1 diopters, in study 1 and study 3, respectively.
- Adverse Events (AEs)
  - The safety analysis conducted by the FDA included 512 eyes (293 eyes with keratoconus, 219 eyes with corneal ectasia) in 364 patients who received CXL treatment. 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 AEs resolved during the first month, but corneal epithelium defect, corneal striae, punctate keratitis, photophobia, dry eye, eye pain, and reduced visual acuity took up to 6 months to resolve, and corneal opacity took up to 12 months. However, in 1% to 6% of patients, these AEs could continue beyond 12 months. Corneal opacity was still present at 12 months in 6% of corneal ectasia patients (Center for Drug Evaluation and Research, 2015).

**Table 1.**

| Summary of Pivotal Trial Characteristics and Results Study | Study | Design | Dates | Patients (N or n) Total = 384 | Difference in Mean Change in Kmax From Baseline to 12 Months (95% CI) |
|---|---|---|---|---|---|
| **Unpublished** | UVX-001 | RCT | 2008-2010 | Keratoconus (58)<br>Ectasia (49) | -1.9 D (-3.4 to -0.3)<br>-2.0 D (-3.0 to -1.1) |
| **Hersh et al (2011)** | UVX-002 | RCT | 2008-2010 | Keratoconus only (147) | -2.3 D (-3.5 to -1.0) |
| Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with Progressive Keratoconus; ClinicalTrials.gov Identifier: NCT00647699<br>In UVX-002: Hershet al (2011) reported early trial results 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 noted. | | | | | |
| **Hersh et al (2011)** | UVX-003 | RCT | 2008-2011 | Ectasia only (130) | -1.1 D (-1.9 to -0.3) |
| Safety and Effectiveness of the UV-X System for Corneal Collagen Cross-Linking in Eyes with Corneal Ectasia After Refractive Surgery; ClinicalTrials.gov Identifier: NCT00674661<br>In UVX-003: 4 patients in the collagen cross-linking group had missing baseline Kmax values and were excluded from the analysis. | | | | | |

Abbreviations: CI: confidence interval; D: diopter; Kmax: maximum corneal curvature; RCT: randomized controlled trial

Wittig-Salva et al. (2014) reported 3 year refractive, topographic, and clinical outcomes following CXL in 94 eyes with progressive keratoconus from a prospective RCT. The primary outcome measure was the maximum simulated keratometry value (Kmax). In control eyes (n=48), Kmax increased by a mean of 1.20±0.28 diopters (D), 1.70±0.36 D, and 1.75±0.38 D at 12, 24, and 36 months, respectively (all P <0.001). In treated eyes (n=46) , Kmax flattened by -0.72±0.15 D, -0.96±0.16 D, and -1.03±0.19 D at 12, 24, and 36 months, respectively (all P <0.001).The treated eyes had better uncorrected visual acuity (UCVA; measured in logMAR units) and best spectacle-corrected visual acuity (BSCVA) than control eyes. The authors concluded that at 36 months, there was a sustained improvement in Kmax, UCVA, and BSCVA after CXL, whereas eyes in the control group demonstrated further progression.

Hersh et al. (2017) reported 205 participants with keratoconus treated with CXL (n=102) or a sham procedure (n=103) from a phase 3, prospective, RCT. 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. 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). 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) published the results of a 2-year randomized trial that compared CXL with 1 month of riboflavin eye drops in 39 eyes of 31 keratoconus patients. All patients received intrastromal corneal ring segments after 3 months. Patients were examined 1- and 3-months following treatment with CXL or riboflavin, as well as 1, 3, 6, 12, 24 months after intrastromal corneal ring segment implantation. During the 24-month follow-up, there were no significant differences between the two groups in terms of uncorrected visual acuity, best-corrected visual acuity, or three topographic parameters (flattest K, steepest K, and average keratometry).

**Systematic Reviews**

Chunyu et al. (2014) published a systematic review and meta-analysis of the effectiveness of CXL in progressive keratoconus. A total of 1171 participants (1557 eyes) were enrolled in this meta-analysis were included in this analysis. Some of the published literature, including a few small, RCTs demonstrated good results after CXL, but large RCTs with long-term follow-up to establish a cause-effect relationship are lacking. The systematic review and meta-analysis concluded that CXL may be effective in halting the progress of KC for at least 12 months under certain conditions and the effects of CXL on visual acuity improvement are also remarkable. However, it was noted that with long-term follow-up (after 18 months post-CXL), a significant decrease in Kave and MRSE was observed and BCVA also significantly increased compared with the pre-CXL values. However, no statistical difference in corneal thickness after CXL was found during long-term follow-up. Further research from randomized trials is necessary to confirm these findings.

Sykakis et al. (2015) conducted a Cochrane study assessing CXL as a therapy for keratoconus. The August 2014 literature search did not include every phase 3 trial submitted to the FDA (as addressed above). Reviewers included 3 small RCTs done in Australia, the United Kingdom, and the United States, with a total of 225 eyes enrolled and 219 eyes evaluated. All 3 trials had a high probability of performance bias (lack of masking), detection bias (just one trial attempted to mask outcome evaluation), and attrition bias (incomplete follow-up). Due to discrepancies in measuring and reporting outcomes, the reviewers did not conduct a meta-analysis. The evidence supporting the use of CXL in the treatment of keratoconus is limited due to a paucity of well conducted RCTs. Overall, the quality of the evidence was considered to be very low, mostly as a result of downgrading the evidence due to the risk of bias in the included studies, imprecision, indirectness, and publication bias.

Meiri 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 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 while CXL appeared to be effective at halting the deterioration of keratoconus, it was only slightly effective at improving visual acuity.
McAnena et al (2017) conducted a systematic review/meta-analysis of 13 studies (n = 490 eyes) to assess the effects of standard, trans-epithelial or accelerated CXL treatment for keratoconus in pediatric patients, 18 years or younger (average age: 15 years). Two-year data were available for 3 studies (n=131 eyes) and the improvement in BCVA remained significant. The review documented that standard CXL seems to be effective in halting the progression of keratoconus in pediatric patients and may be effective at stabilizing topography and improving both best-corrected and uncorrected visual acuity at 1 year in pediatric patients. At 12 months, all three measures in the trans-epithelial group remained stable. At one year, the findings indicated that conventional CXL may be beneficial in halting the progression of keratoconus in pediatric patients. Larger, long-term studies are required to determine its efficacy.

According to UpToDate, CXL has been proposed as a treatment for progressive keratoconus (Grade 2B recommendation is a weak recommendation; alternative approaches may be better for some patients under some circumstances). It has been shown to slow the progression of the disease by strengthening collagen fibers. CXL is not recommended for patients who have advanced illness. Correction of visual impairment in some keratoconus patients may also involve spectacles, contact lenses, or surgical interventions (UpToDate 2022).

Hayes conducted a general comparative effectiveness assessment of CXL for the treatment of progressive keratoconus in adolescent and adult patients, utilizing an evidence base consisting of nine RCTs (annual review: Jan 13, 2022). Conventional CXL for the treatment of progressive keratoconus in adolescent and adult patients received rating of C, indicating that a moderate-sized body of low-quality evidence supports some positive outcomes regarding the benefits of C-CXL. Available studies have 1 to 3-year follow-up intervals. CXL may reduce or halt keratoconus progression by modifying corneal topography (i.e., flattening the cornea), however results are inconsistent. Furthermore, it is unknown how CXL affects visual acuity and corneal thickness results. Additional, larger RCTs with long-term evaluation of treatment results over 3 years will provide definitive conclusions on the safety and efficacy of CXL for the treatment of progressive keratoconus. An additional gap in the evidence base is the lack of studies reporting on quality-of-life measures regarding conventional C-CXL and alternatives for the treatment of progressive keratoconus.

**National and Specialty Organizations**

**American Academy of Ophthalmology (AAO)** published a Preferred Practice Guideline pertaining to corneal ectasia in 2013 (AAO, 2013). The AAO noted that CXL 'has the potential to reduce the risk of progressive ectasia (particularly in its early stages) and stabilize the corneal contour. This is the case particularly in mild to moderate keratoconus, and it may also hold promise in cases of corneal ectasia occurring after keratorefractive surgery.' The AAO stated that 'The use of corneal mapping and the use of newer contact lens technologies may provide an alternative to surgery for treatment of corneal ectasia. Current CXL protocols require either the removal of the epithelium or exposure of the intact epithelium to agents that increase the permeability of the cell layer, followed by the application of topical riboflavin and UV-A treatment.'

**National Institute for Health and Care Excellence (NICE)** updated its 2009 recommendations on corneal CXL using riboflavin and ultraviolet A in 2013 in its interventional procedures guidance titled 'Photochemical corneal collagen cross-linkage using riboflavin and UVA for keratoconus and keratectasia.' NICE noted that most of the evidence for CXL utilizing riboflavin and UVA for keratoconus was for epithelium-off CXL, with little evidence for transepithelial CXL and any combination procedures. The conclusions and recommendations of NICE included the following (2013):

- Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia is adequate in quality and quantity.
- Current evidence on the safety and efficacy of epithelium-on (transepithelial) CXL and combination procedures is lacking in quantity and quality.
- In selecting patients for these treatments, corneal thickness and the probability of disease progression should be considered.

## SUPPLEMENTAL INFORMATION

**Cornea:** The outermost layer of the eye; dome shaped and covers the front of the eye.

**Ectasia:** A condition that occurs when the cornea is so thin that pressure within the eye leads to bulging of the cornea.

**Keratoconus:** Cone-shaped cornea with the apex of the cone being forward; also called conical cornea

**Keratometry (K):** Measurement of the curvature of the cornea

**Manifest cylinder:** A subjective measure of a change in the cylinder (astigmatism). For example, an increase of 1.00 D or more in manifest cylinder indicates that the glasses prescription astigmatism has changed by 1 or more.

**Manifest refraction spherical equivalent (MRSE):** A subjective measure of a change in the cylinder (astigmatism). It is calculated arithmetically by adding the sphere power and half of the cylinder power. MRSE is used in the calculation of spherical equivalent.

## CODING & BILLING INFORMATION

### CPT Codes

| CPT | Description |
|---|---|
| **0402T** | Collagen cross-linking of cornea including removal of the corneal epithelium and intraoperative pachymetry when performed (Report medication separately) |
| **J2787** | Riboflavin 5'-phosphate, ophthalmic solution, up to 3 mL (Photrexa) (new code effective 1/1/19) [Photrexa, Photrexa Viscous] |

### HCPCS Code

| HCPCS | Description |
|---|---|
| **J2787** | Riboflavin 5'-phosphate, ophthalmic solution, up to 3 mL [Photrexa, Photrexa Viscous] |

**AVAILABLE DOSAGE FORMS:** Photrexa-Photrexa Viscous Kit: Photrexa 0.146%; Photrexa Viscous 0.146% in Dextran 20% (6 mL) [contains dextran]

**CODING DISCLAIMER.** Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

## APPROVAL HISTORY

| | |
|---|---|
| **8/10/2022** | Policy reviewed and updated. No changes to coverage criteria. Updated references. Removed references to Photrexa Viscous in policy due to discontinuation of product. |
| **8/11/2021** | Policy reviewed. No changes to coverage criteria. Updated references. |
| **7/2020** | New Policy. IRO Peer Review. 7/7/2020. Practicing Physician. Board certified in Ophthalmology. Added Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%, and Photrexa (riboflavin 5'phosphate ophthalmic solution) 0.146%, to be used with the KXL System for the FDA approved indications. All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were revised with the most recent medical literature and available evidence. |
| **6/19/2019** | Policy retired. IRO Peer Review: 10/29/18. Policy reviewed by practicing MD board certified in Ophthalmology. |
| **12/19/2018** | New policy. IRO Peer Review. Policy reviewed by practicing MD board certified in Ophthalmology. |

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## APPENDIX

***Reserved for State specific information.*** *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

**OHIO MEDICAID**: All Ohio Medicad prior authorization requests are reviewed for medical necessity on an individual basis.