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

Last Approval: 8/9/2023
Next Review Due By: August 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Keratoconus is a corneal dystrophy distinguished by localized thinning of the corneal stroma with secondary ectasia (Wayman 2022). This results in progressive myopia and irregular astigmatism with associated progressive loss of vision and reduced quality of life (AAO 2023). 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 (AAO 2023). Keratoplasty is typically reserved for advanced disease with suboptimal vision and contact lens wear tolerance (Hayes 2022). 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 (Hayes 2022).

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 (AAO 2023). 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 (Hayes 2022). Ectasia occurs postoperatively and primarily affects older populations (AAO 2018). Almost invariably the cause is refractive eye surgery, most commonly laser in situ keratomileusis (LASIK) surgery and photorefractive keratectomy (PRK) (AAO 2018). 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 corneal cross-linking (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) (Hayes 2023). 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 (AAO 2018). According to Hayes (2022), “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 (Hayes 2022). Corneal transplantation is the only option available when functional vision can no longer be achieved (Hayes 2023).

CXL is an in-office procedure FDA-approved to treat progressive keratoconus and corneal ectasia to preserve visual function (AAO 2022). 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 (Wayman 2022). 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 (AAO 2022; Hayes 2022). 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 penetrate the corneal tissue more easily (AAO 2022). Riboflavin eye drops are applied to the corneal surface before the procedure and intermittently during the procedure (AAO 2023). The corneal surface is then exposed to UVA radiation (AAO 2023). 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. According to Wayman (2022), "CXL is generally not performed in patients with active or history of herpes simplex virus keratitis, thin corneas, or corneal hydrops." **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 (CDER 2016). 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 "corneal ectasia following refractive surgery" (FDA 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 (AAO 2018). The AAO (2022) stated that "studies thus far have demonstrated lower effectiveness of CXL in this method." **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 (Hayes 2023). The evidence basis for these combination procedures (also known as "CXL-plus") is limited (Hayes 2023).

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. Studies suggest improvements in corneal thickness and visual acuity with CXL that has been maintained at two to three years (Moghadam et al. 2019).
- 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 2016).

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 [Hersh et al. 2017]

   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 [Hersh et al. 2017]

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 2018]
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 2023)

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 (CDER 2014):

- **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 (CDER 2016).
- **Corneal ectasia following refractive surgery:** Treatment of corneal ectasia following refractive surgery with the KXL System in corneal collagen cross-linking (FDA 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. CXL appears to be generally safe, with impaired epithelial healing and corneal haze as the most reported complications. A summary of relevant studies is discussed below.

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, open-label, sham-controlled trials with 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 debridement or have the UVA light source turned on. For sham subjects who received CXL treatment at month 3 or month 6, the last maximum keratometry (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 D and -1.1 D, 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 (CDER 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) Ectasia (49)	-1.9 D (-3.4 to -0.3) -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 In UVX-002: Hersh et 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 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

Moghadam et al. (2019) conducted a prospective interventional study of patients with advanced progressive keratoconus with a Kmax of greater than 58 D. A total of 30 eyes amongst 27 participants were included in the study. Inclusion criteria included age > 12 years and a definitive diagnosis that was an indication for CXL. Exclusion criteria included pregnant and lactating women, corneal scarring due to severe keratoconus, and "patients with a positive history of systemic disease, previous corneal and intraocular surgery, a history of chemical damage or delay in corneal epithelium repair, or a neurological or retinal disease causing reduced vision." Researchers obtained each participant's BCVA and uncorrected visual acuity prior to CXL procedure and also performed a slit lamp examination, ophthalmoscopy, and obtained imaging using a Pentacam. Each CXL procedure was completed by the same surgeon that utilized the Dresden protocol on all participants. Hypotonic riboflavin was administered if the participant's corneal thickness was < 400 microns following epithelial removal and the same solution was then administered every 3 minutes for 30 minutes. Three patients had bilateral CXL performed and 24 had unilateral CXL. Follow-up was completed at 1 week and then 1, 3, 6, 12, and 24 months after CXL. The same examinations completed on enrollment were completed at each follow-up visit with the exception of Pentacam imaging. The Pentacam imaging was obtained at the 12- and 24-month follow-up visits. The mean uncorrected visual acuity improved from 0.73±0.36 minimum angle of resolution (logMAR) to 0.47±0.31 logMAR at 12 months and 0.48±0.30 logMAR at 24 months. The mean BCVA improved from 0.59±0.34 logMAR at baseline to 0.44±0.33 logMAR at 12 months and 0.45±0.32 logMAR at 24 months. The mean Kmax improved from 62.19±4.56 D at baseline to 60.91±4.36 D at 12 months and 60.95±4.42 D at 24 months. The thinnest point thickness at baseline was 438.65±40.11 microns, 430.46±41.05 microns at 12 months, and 431.43±61.92 microns at 24 months. Only one eye was reported as a treatment failure due to an increase in Kmax of > 2.0 D. There were no complications reported in this study. Results showed that CXL was able to safely stabilize visual acuity and tomographic parameters. Limitations of this study included a small sample size, no control group, and nonrandomization of patients.

Shajari et al. (2018) completed a meta-analysis of 22 studies to compare the results of conventional CXL (C-CXL) to accelerated CXL (A-CXL) for the treatment of progressive keratoconus. There were a total of 1158 eyes included in the meta-analysis with 577 eyes in the C-CXL group and 581 eyes in the A-CXL group. The primary outcomes observed were clinical results and changes in corneal properties. These outcomes were reported in the form of uncorrected

distance visual acuity, corrected distance visual acuity, spherical equivalent, spherical and cylindrical error, central and minimum corneal thickness, corneal hysteresis, corneal resistance factor, anterior stromal keratocyte density, sub basal nerve density, endothelial cell density, average keratometry (Kmean), Kmax, minimum keratometry (Kmin), demarcation line of depth, and time of reepithelialization. Inclusion criteria included studies that compared C-CXL and A-CXL and reported at least one of the primary outcomes. Exclusion criteria included ex vivo and pediatric studies and studies that combined CXL with photorefractive keratectomy for treatment. The meta-analysis only included studies with a corneal thickness > 400 microns as most of the studies considered a corneal thickness < 400 microns to be an exclusion criterion. Similar changes in uncorrected distance visual acuity were noted in both groups until 12 months where C-CXL was noted to show greater improvement. No significant difference was noted between either group for spherical error until the 3- and 6-month visits where C-CXL was noted to be superior. A-CXL was noted to be superior in improving spherical error after 6 months. There was no significant difference between either group in spherical equivalent until the last follow-up visit where C-CXL was noted to be superior. C-CXL was noted to be superior for cylindrical error correction in all visits except for the 3-month visit where no significant difference was noted between either group. No significant differences in Kmin, Kmean, or Kmax were noted between either group until the last follow-up where C-CXL was noted to be superior for corneal flattening (Kmax and Kmin). A higher early decrease was noted in central corneal thickness for the C-CXL group before continuing with a less significant decrease until the last follow-up visit. Central corneal thickness remained stable in the A-CXL group. Greater decreases in minimum corneal thickness were noted in the C-CXL group. Smaller reductions in corneal hysteresis and corneal resistance factor were noted in the C-CXL group. Both groups showed similar changes in sub basal nerve density. There were no significant differences in time of reepithelialization between either group. A greater change in endothelial cell density was noted at 1 month in the A-CXL group and then the C-CXL group at 6- and 12-months. A distinct greater reduction in anterior stromal keratocyte density was noted in the C-CXL group. Deeper demarcation lines were noted in the C-CXL group. Minimal complications were noted with 2 cases of delayed epithelial healing in the C-CXL group and 4 cases in the A-CXL group. Anterior stromal scarring was noted in 2 eyes in the A-CXL group. Trace or mild haze was reported in 10 eyes in the C-CXL group and 10 eyes in the A-CXL group. There was only one case of severe central haze in the C-CXL group. Researchers noted that both C-CXL and A-CXL can successfully strengthen corneal tissue.

Hersh et al. (2017) completed a phase 3, prospective RCT involving 205 participants with keratoconus treated with CXL (n=102) or a sham procedure (n=103). Inclusion criteria included age ≥ 14 years, axial topography pattern consistent with corneal ectasia (including relative inferior steepening with inferior:superior difference ≥ 1.5 D), corrected distance visual acuity worse than 20/20, and corneal thickness of ≥ 300 microns as measured on Pentacam. Participants that had a history of corneal surgery other than laser refractive surgery were excluded. This included a corneal pachymetry < 300 microns, and a history of corneal disease that would interfere with healing, 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 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 CXL treatment after 3 months; thus, their data were imputed based on the last observation carried forward method. Also, patients in the control group did not undergo removal of their epithelium.

National and Specialty Organizations

American Academy of Ophthalmology (AAO) published a Preferred Practice Pattern pertaining to corneal ectasia in 2018 (AAO 2018). The AAO noted that CXL reduces the risk of progressive ectasia (particularly in its early stages) and stabilizes the corneal contour, particularly in mild to moderate keratoconus. Evidence also supports CXL for patients with corneal ectasia after keratorefractive surgery. Prior to keratorefractive surgery, topography and tomography should be performed. A recommendation was also made for corneal topography and tomography following a period of contact lens abstinence when there is evidence of irregular astigmatism or any abnormalities that may indicate keratoconus or any type 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.

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 (Current Procedural Terminology) 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 (Healthcare Common Procedure Coding System) 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

08/09/2023	Policy reviewed, no changes to criteria. Updated Overview, Summary of Medical Evidence, and References. Grammatical edits to Disclaimer section and Documentation Requirements disclaimer. IRO Peer Review on July 19, 2023, by practicing, board-certified physician with a specialty in Ophthalmology.
08/10/2022	Policy reviewed and updated. No changes to coverage criteria. Updated references. Removed references to Photrexa Viscous in policy due to discontinuation of product.
08/11/2021	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.
06/19/2019	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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