Subject: Corneal Collagen Cross-Linking (CXL)	**Original Effective Date:** 12/19/2018
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Contents

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This Molina clinical policy is intended to facilitate the Utilization Management process. 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 (i.e., 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 Molina clinical policy document and provide the directive for all Medicare members.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

This policy addresses corneal collagen cross-linking (CXL, also known as 3-CR or C3R) using riboflavin and ultraviolet A for the treatment of progressive keratoconus or corneal ectasia resulting from refractive surgery. Corneal collagen cross-linking using riboflavin and ultraviolet A is considered investigational for all other indications.

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 Wen et al. 2018). It is one of the most common corneal diseases, affecting approximately 1 in 375 individuals and occurs in all races (Godefrooij DA, et al. 2017)

- Management depends on the severity of the disease. In mild cases, spectacles or soft contact lenses may be adequate but with advanced disease, rigid gas permeable and scleral contact lenses are often required. Keratoplasty is usually reserved for advanced disease with suboptimal vision and impaired wearing tolerance with contact lenses (Mandathara PS et a. 2017; Daizong Wen et al. 2018). Initial treatment usually consists of hard contact lenses which flatten the corneal and help it maintain its shape. As the disease progresses or if the patient does not tolerate the contact lens therapy, a penetrating keratoplasty (i.e., corneal graft/transplant) is the next line of treatment.
- As an alternative, a variety of keratorefractive procedures have been attempted, broadly divided into subtractive and additive techniques. These therapies are intended to reduce some of the complications from a corneal transplant. Subtractive techniques include LASIK. In general, results of this technique have been poor. Intracorneal ring segments (Intacs) can be surgically implanted into the corneal stroma in order to support the corneal cone and flatten the central cornea and is another technique intended to reinforce the cornea, prevent further deterioration, and potentially obviate the need for a penetrating keratoplasty. Intracorneal ring segments can improve vision and contact lens tolerance and delay the need for corneal transplantation, but the long-term stability of the results is uncertain (Vega-Estrada et al. 2016). Approximately 20% of patients with keratoconus will require corneal transplantation (O'Brart DP 2014). These treatments attempt to improve the refractive errors, however, none of these treatments changes the course of the disease, and patients with advanced disease often need corneal transplantation for visual rehabilitation (Hayes 2020).

Corneal Ectasia (also known as keratectasia, iatrogenic keratoconus, or secondary keratoconus) is a long-term condition similar to keratoconus (characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of visual acuity), however 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). After LASIK, the cornea has been made thinner. Because the corneal "wall" has been made thinner, internal pressure from within the eye can cause expansion or distension of the cornea. Treatment options for ectasia include intraocular pressure-lowering drugs and intracorneal ring segments and penetrating keratoplasty is often required.

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.

<u>Corneal collagen cross-linking (CXL) for Keratoconus and Ectasia</u>

CXL is in-office photochemical procedure approved by the Food and Drug Administration (FDA) for the treatment of progressive keratoconus and corneal ectasia. CXL strengthens the cornea if it has been weakened by keratoconus, other corneal disease, or (rarely) a complication of LASIK surgery. Corneal collagen cross-linking is a technique that induces cross-links in the collagen of the corneal stroma by photosensitizing it with riboflavin

and exposing it to ultraviolet-A (UVA) light resulting in increased biomechanical rigidity of the corneal stroma (Wollensak et al. 2003a,b; Wollensak & Iomdina 2009). Thus, by increasing corneal rigidity, the treatment acts to stop, or reverse the progressive thinning and deformation of cornea seen in keratoconus and other corneal ectasias such as that seen post-LASIK surgery. The mechanism of action of the CXL procedures is not fully understood; they may increase the number of 'anchors' that bond collagen fibers together and strengthen the cornea (NICE, 2013). This is expected to stop the progression of the disease, but the duration of benefit is uncertain. The goal of CXL treatment is to halt or diminish the progressive thinning and steepening of the cornea that occurs in keratoconus and in patients with corneal ectasia after refractive surgery and to achieve visual rehabilitation (Gomes et al., 2015).

According to the National Institute for Health and Care Excellence (NICE), there are two different methods of cross-linking the collagen in the cornea:

1) **Epithelium-off collagen crosslinking (CXL) (also known as "epi-off"):** In epithelium-off CXL, the epithelium is first abraded to allow penetration of riboflavin into the corneal tissue (NICE, 2013). 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 (HSV) keratitis, thin corneas, or corneal hydrops (UpToDate 2020).
   The epi-off procedure is currently FDA approved and available as the KXL UV-illumination system and the Photrexa and Photrexa Viscous riboflavin solutions (Avedro). FDA approval of Photrexa Viscous and Photrexa for use in CXL was based on the results of three unpublished, randomized, open-label, sham-controlled trials that demonstrated CXL-treated eyes had significant reductions in corneal curvature at 6 and 12 months compared to sham-treated eyes.
2) **Epithelium-on CXL (also referred to as "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 (epithelium-off or epithelium-on CXL) can be combined with other interventions such as intrastromal corneal ring segments, photorefractive keratectomy (PRK) or phakic intraocular lens implantation to improve visual acuity. The evidence base for these combination procedures (known as 'CXL-plus') is also limited (NICE, 2013).

Summary of Evidence: Epithelium-off CXL ("epi-off") Treatment

- CXL using riboflavin 5'-phosphate ophthalmic solution (Photrexa Viscous, Photrexa) with UVA irradiation (KXL System) has been shown to decrease clinical progression and improve visual acuity in patients with progressive keratoconus or post-refractive surgery corneal ectasia. However, to what extent it will permit patients to avoid corneal transplantation is unclear. Although there is evidence from RCTs that CXL reduces, and in some cases, reverses the corneal steepening that leads to a reduction in visual acuity in the short-term, there is uncertainty regarding the long-term outcomes of corneal CXL for the treatment of keratoconus.

- Relevant outcomes include change in disease status, functional outcomes, and treatment-related morbidity. Evidence from RCTs, including several pivotal trials discussed in this policy, supports the short-term improvements of CXL in corneal steepening and visual acuity compared with untreated eyes. Results from 1 trial have reported that these benefits are maintained at 2 to 3 years
- Some retrospective studies have reported positive outcomes to 10 years, although these reports have small sample sizes at long-term follow-up and limited information on the entire population of patients treated with corneal CXL during the same time period. Prospective studies with larger numbers of patients who are followed over many years may provide evidence of results in the long-term. Longer-term outcomes from large cohorts will also be useful to evaluate potential long-term complications of this new treatment approach.
- Further research is needed to determine whether corneal CXL improves longer-term outcomes as well as evaluating other vital aspects 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, outcomes based on the original corneal thickness versus corneal thickness after treatment was <400 microns or > 400 microns (CDER, NDA 203324).

REGULATORY STATUS

US Food and Drug Administration (FDA): Orphan drug designation: Treatment of keratoconus (April 2016) and treatment of corneal ectasia following refractive surgery (July 2016)

On April 15, 2016, 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.**

On July 15, 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).

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:

- **Corneal ectasia following refractive surgery:** Treatment of corneal ectasia following refractive surgery with the KXL System in corneal collagen cross-linking

- **Keratoconus, progressive:** Treatment of progressive keratoconus with the KXL System in corneal collagen cross-linking

NOTE: Photrexa and Photrexa Viscous are for use with the KXL System only. Photrexa and Photrexa Viscous are administered during the CXL procedure. Refer to the prescribing information for specific dosage and administration instructions.

Available as: Photrexa Viscous and Photrexa 0.146% ophthalmic solutions are supplied in cases of 10 3-mL single-use syringes. The KXL System is available separately.

CLASSIFICATION: Corneal Collagen Cross-Linking Agent, Ophthalmic; Ophthalmic Agent

RECOMMENDATION

Epithelium-off, corneal collagen crosslinking (C-CXL) using a U.S. FDA approved drug/device system (e.g., Photrexa® Viscous or Photrexa® with the KXL® System) may be authorized for progressive keratoconus or corneal ectasia following refractive surgery if ALL the following criteria are met: [ALL]

1. Prescriber specialty [ONE]

- ❒ Prescribed by board-certified ophthalmologist or cornea specialist who specializes in the surgical treatment of keratoconus

- ❒ 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

2. Diagnosis/Indication [ALL]

Prescriber submit ALL supporting documentation and clinical rationale (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*): [ALL]

- ❒ Diagnosis of ONE of the following supported by clinical documentation: [ONE]

  - ❍ Progressive keratoconus (thinning of the cornea)

  - ❍ Corneal ectasia (corneal thinning and protrusion) after refractive surgery [e.g., LASIK or photorefractive keratectomy (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.

- ❒ Member meets ONE of the following (A OR B) according to specific diagnosis: [A OR B]

  A. **Progressive Keratoconus [ALL]**

  1) AT LEAST ONE of the following changes have occurred within the 24 months: [ANY]
     - ❍ Increase of 1.00 diopters (D) or more in the steepest keratometry measurement; or
     - ❍ Increase of 1.00 D or more in manifest cylinder; or
     - ❍ Increase of 0.50 D or more in manifest refraction spherical equivalent (MRSE)

     AND

  2) Corrected distance visual acuity (CDVA) worse than 20/20 with properly fitted spectacles or contact lenses

     AND

  3) Corneal thickness 300 microns or more

B. Corneal ectasia resulting from refractive surgery (e.g. LASIK)

1) Corrected distance visual acuity (CDVA) worse than 20/20
   AND
2) Corneal thickness of at least 300 microns at the thinnest area

3. Age/Gender/Restrictions [ALL]

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

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]
Documentation of ALL the following must be submitted for review:

- ❒ Absence of visual disturbance from a significant central corneal opacity or other eye disease (e.g., herpetic keratitis, neurotrophic keratopathy)
- ❒ 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

5. Contraindications/Exclusions [ANY]
Authorization for CXL will not be authorized if ANY of the following conditions apply [ANY]
Contraindications/Exclusions (AAO, 2017b)

- ❒ Corneal thickness of < 300 microns
- ❒ Prior herpetic infection (because viral reactivation may occur)
- ❒ Concurrent infection
- ❒ Severe corneal scarring or opacification
- ❒ History of corneal surgery, including intracorneal ring segments
- ❒ 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
- ❒ Severe ocular surface disease (e.g., dry eye)
- ❒ Autoimmune disorders

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included. **NOTE:** Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

- ❒ Requested therapy for use in which affected eye: [AS APPLICABLE]
  - ❍ Right eye
  - ❍ Left eye

EXCLUSIONS

C-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).

SUMMARY OF MEDICAL EVIDENCE

Corneal Collagen Cross-Linking (CXL)

The peer-reviewed medical evidence for corneal 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 ultraviolet-A (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 randomized controlled trials (Wollensak G.; Hoyer A, et al. ; Meiri Z, et al. 2016; McAnena L, et al. 2017; Padmanabhan P, et al. 2017)

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

Photrexa Viscous/Photrexa

FDA approval of Photrexa Viscous and Photrexa for use in CXL was based on the results of three unpublished, randomized, open-label, sham-controlled trials in a total of 384 patients ≥14 years old with progressive keratoconus (studies 1 and 2) or with corneal ectasia following refractive surgery (studies 1 and 3). 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. In all 3 trials, only 1 eye per patient was designated as the experimental eye. Study 1 enrolled 49 patients and study 3 enrolled 130 patients with corneal ectasia.

- Primary end point was a 1-diopter (D) reduction in the maximum corneal curvature (Kmax) at month 3; however, because corneal stromal remodeling associated with healing response after CXL requires 6 to 12 months to stabilize, the time point for primary end point was changed from 3 to 12 months. This end point was better suited for evaluating the long-term clinical benefits of the CXL treatment. Maximum corneal curvature (Kmax) was accessed at baseline and at 12 months.
- Patients with corneal ectasia diagnosed after laser in situ keratomileusis (LASIK) or photorefractive keratectomy or those with progressive keratoconus were included in these trials. Progressive keratoconus was defined as 1 or more of the following over a period of 24 months or less before randomization:
    - An increase of 1 D in the steepest keratometry value,
    - An increase of 1 D in regular astigmatism evaluated by subjective manifest refraction,
    - A myopic shift (decrease in the spherical equivalent) of 0.50 D on subjective manifest refraction,
    - A decrease ≥0.1 mm in the back optical zone radius in rigid contact lens wearers where other information was not available.
- Sham-control eyes were treated with a topical anesthetic and riboflavin solution (1 drop every 2 minutes for 30 minutes) but did not undergo epithelial débridement or have the ultraviolet A (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 (95% CI: -3.0, -1.1) and -1.1 diopters (95% CI: -1.9, -0.3), in study 1 and study 3, respectively.

Adverse Events

- 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 adverse events 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 adverse events 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

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: 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 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

Other Randomized Controlled Trials

Wittig-Silva et al (2008; 2014) reported the first RCT of corneal CXL in 2008 and published three-year results in 2014.

A prospective randomized, controlled trial reported the refractive, topographic, and clinical outcomes 3 years after corneal collagen cross-linking (CXL) in eyes with progressive keratoconus.

- 100 eyes with progressive keratoconus were randomized into the CXL treatment or control groups; 50 eyes randomized to CXL treatment and 50 randomized to untreated control
- To be eligible for enrollment, clear evidence of progression of ectasia over the preceding 6 to 12 months was required. Progression was confirmed if at least 1 of the following criteria were met: an increase of at least 1 D in the steepest simulated keratometry reading (K-max); 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.
- The primary outcome measure was the maximum simulated keratometry value (Kmax). Other outcome measures were uncorrected visual acuity (UCVA; measured in logarithm of the minimum angle of resolution [logMAR] units), best spectacle-corrected visual acuity (BSCVA; measured in logMAR units),

sphere and cylinder on subjective refraction, spherical equivalent, minimum simulated keratometry value, corneal thickness at the thinnest point, endothelial cell density, and intraocular pressure.

- At the time of analysis for the 2008 report, 20 eyes had reached 1-year follow-up. The 3-year results included 46 CXL-treated and 48 control eyes. Last observation carried forward (LOCF) was used for 26 eyes, including 17 eyes from the control group with progressive disease that underwent compassionate-use CXL or corneal transplantation. In the CXL group, there was a flattening of K-max by -1.03 D, compared with an increase in K-max of 1.75 in the control group. One eye in the CXL group progressed by more than 2 D, compared with 19 eyes in the control group. Uncorrected visual acuity (UCVA) and BCVA improved in the CXL-treated eyes at 1, 2, and 3 years. In control eyes, UCVA was significantly reduced at 36 months ($p=0.034$) and there was a trend of a decrease in BCVA ($p=0.10$). The difference between groups in UCVA was significant ($p<0.001$). Follow-up is continuing through 5 years.
- There was a significant reduction in corneal thickness measured using computerized videokeratography in both groups at 36 months (control group: -17.01±3.63 μm, $P <0.001$; treatment group: -19.52±5.06 μm, $P <0.001$) that was not observed in the treatment group using the manual pachymeter (treatment group: +5.86±4.30 μm, $P = 0.181$). The manifest cylinder increased by 1.17±0.49 D ($P = 0.020$) in the control group at 36 months. There were 2 eyes with minor complications that did not affect the final visual acuity.
- 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.

Renesto et al. (2010) reported 2-year results of a randomized trial that compared CXL versus 1 month of riboflavin eye drops in 39 eyes of 31 patients with keratoconus (Renesto et al. 2010). After 3 months, all patients received intrastromal corneal ring segments (ICRS). Patients were evaluated at 1 and 3 months after treatment with CXL or riboflavin, and then at 1, 3, 6, 12, and 24 months after ICRS insertion. There was no significant difference between the 2 groups for UCVA, BCVA, or in 3 topographic parameters (flattest K, steepest K, and average keratometry) throughout the 24-month follow-up.

Systematic Reviews

A Cochrane review, 'Corneal collagen cross-linking for treating keratoconus' (Sykakis et al. 2015), published in March 2015 evaluated the use of corneal CXL for the treatment of keratoconus and included results from three RCTs comparing CXL with sham treatment in adults. The literature search was conducted in August 2014 and did not include all phase 3 trials submitted to the FDA. A total of 219 treated eyes were included. They report that CXL-treated eyes were less likely to progress [an increase of 1.5D or more in maximum keratometry (Kmax)] than sham-treated eyes and that, on average, CXL-treated eyes had less steep corneas and better uncorrected visual acuity at 12 months. The overall quality of the evidence was judged to be very low, primarily due to downgrading the evidence due to the risk of bias in the included studies, imprecision, indirectness, and publication bias. They concluded that although the size of the potential treatment effect was large, the evidence for the use of CXL in keratoconus is limited due to the risk of bias, imprecision and indirectness of the published RCTs.

Chunyu et al. published a systematic review and meta-analysis of the effectiveness of CXL in progressive keratoconus. 1171 patients with a total of 1557 treated eyes were included in their analysis. They showed improvements in uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) and significant flattening of Kmax up to and beyond 18 months. They concluded that CXL was effective in stabilizing the progression of keratoconus with improvements in visual acuity and key topographic values.

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 CXL treatment.[16] Reviewers reported a modest but statistically nonsignificant improvement in visual acuity of 1 to 2 Snellen lines at 3 months or more after undergoing CXL. Reviewers concluded that, although CXL appeared to be effective at halting the deterioration of keratoconus, it was only slightly effective at improving visual acuity.

McAnena et al (2017) reported on the results of a systematic review and a meta-analysis assessing the efficacy of CXL treatment for keratoconus in pediatric patients. A total of 13 articles, published between May 2011 and December 2014, examining 490 eyes of 401 patients (mean age, 15.25 years), were included in the meta-analysis. Bias assessment of individual studies was not included. Reviewers reported a significant improvement in BCVA at 6 months (standardized mean difference, -0.66; 95% confidence interval [CI], -1.22 to -0.11; p=0.02), which was maintained at 1 year (standardized mean difference, -0.69; 95% CI, -1.15 to -0.22; p<0.01). Two-year data were available for 3 studies (n=131 eyes) and the improvement in BCVA remained significant (standardized mean difference, -1.03; 95% CI, -2 to -0.06; p=0.04). This systematic review and meta-analysis concluded 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. The transepithelial approach may also be effective in stabilizing topography but does not significantly improve visual acuity at 1 year in pediatric patients. Due to the distinctly aggressive and progressive nature of the disease in patients younger than 18 years, with higher risk of needing corneal grafts, it is reasonable to consider CXL treatment in this group.

Peer Reviewed Literature

UpToDate notes that corneal collagen cross-linking is recommended for the management of keratoconus (*Grade 2B recommendation; a weak recommendation; alternative approaches may be better for some patients under some circumstances*). It has been demonstrated to slow the progression by strengthening collagen fibers. In patients with stable disease, advanced ectatic disease (cornea is too thin), or severe scarring, correction of visual impairment may require spectacles, contact lenses, or surgical interventions (UpToDate, 2020).

HAYES (2018) evaluated the evidence from 23 studies, including 9 RCTs, 2 prospective trials with historical controls, 6 prospective comparative cohort studies, and 6 retrospective comparative cohort studies of patients with documented keratoconus. Sample sizes ranged for 50 to 205 eyes comparing sham treatments to epi- on and epi-off procedures and follow-up ranged from 1 to 3 years. Outcome measures included corneal topography, including maximum keratometry (Kmax), average keratometry (Km), keratometry in flat meridian (K1), keratometry in steep meridian (K2); visual acuity, including best-spectacle-corrected visual acuity (BSCVA), corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA); refraction measures, including spherical equivalent (SE), spherical error, cylindrical error; corneal thickness measured by central corneal thickness (CCT) or thinnest point corneal thickness (TPCT); adverse events (AEs)

For the use of conventional corneal cross-linking (C-CXL) for the treatment of progressive keratoconus in adolescent and adult patients, HAYES rating reflects '*a moderately sized body of low-quality evidence that suggests some positive but inconsistent results regarding the benefits of C-CXL. This Rating also reflects the insufficient evidence concerning long-term safety and efficacy of C-CXL compared with no treatment or sham treatment*.'

HAYES noted that while CXL may provide a treatment option for patients with progressive keratoconus, the procedure may carry risks for 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. Availability of additional, larger RCTs with long-term assessment of the results of treatment (> 3 years) will offer definitive conclusions regarding the safety and effectiveness of CXL for the treatment of progressive keratoconus await. In addition, better-quality studies are required to define the patient population that is most likely to respond to CXL is recommended.

Professional Society Guidelines

American Academy of Ophthalmology (AAO) (2013)
The AAO published a Preferred Practice Guideline pertaining to corneal ectasia in 2013 (AAO, 2013). Regarding CXL, the AAO noted that it '*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 further 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, 2013)
NICE issued guidance on corneal collagen cross-linking (CXL) using riboflavin and ultraviolet A (updating its 2009 guidance) in 2013: 'Photochemical corneal collagen cross-linkage using riboflavin and UVA for keratoconus and keratectasia'

NICE noted that much of the evidence for CXL using riboflavin and ultraviolet A (UVA) for keratoconus was for the epithelium-off (C-CXL) approach, with transepithelial CXL (T-CXL) having less evidence, as well as less evidence for any combination procedures at the time of publication. NICE's conclusions and advice therefore included the following (NICE, 2013):

- Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia was adequate in quality and quantity.
- Current evidence on the safety and efficacy of epithelium-on (transepithelial) CXL (T-CXL), and the combination (CXL-plus) procedures was inadequate in quantity and quality since it is a more recent technique and less evidence is available on its safety and efficacy.
- Either procedure (epithelium-off or epithelium-on CXL) can be combined with other interventions, and the evidence base for these combination procedures (known as 'CXL-plus') is also limited.

DEFINITIONS

- 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 INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

HCPCS	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]

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Professional Society Guidelines and Other Publications

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Review/Revision History

12/19/2018: Policy created. Advanced Medical Review (AMR): Policy reviewed by practicing MD board certified in Ophthalmology. 10/29/18

6/19/2019: Policy retired. Advanced Medical Review (AMR): Policy reviewed by practicing MD board certified in Ophthalmology. 10/29/18

7/2020: New Policy. Advanced Medical Review (AMR): Policy reviewed by practicing MD board certified in Ophthalmology. 7/7/2020

Notable Revisions: 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