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

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OVERVIEW

Keratoconus is a corneal dystrophy characterized by localized thinning of the corneal stroma, leading to secondary ectasia (Wayman 2024). This progressive condition results in worsening myopia, irregular astigmatism, and deteriorating visual acuity, significantly impacting quality of life ([3]AAO 2024). Treatment is guided by disease severity. In mild cases, spectacles or soft contact lenses may be sufficient, while more advanced cases often require rigid gas permeable or scleral contact lenses ([3]AAO 2024). Keratoplasty, or corneal transplantation, is typically reserved for patients with advanced disease who experience suboptimal vision or develop intolerance to contact lenses (Hayes 2022). Initially, rigid lenses are used to flatten the cornea and help maintain its shape. As the disease progresses – or if lens therapy fails - penetrating keratoplasty (a full-thickness corneal transplant) may become necessary (Hayes 2022).

Corneal Ectasia following refractive surgery – also known as keratectasia, iatrogenic keratoconus, or secondary keratoconus – is a progressive, long-term condition marked by corneal thinning and steepening, leading to optical irregularities and declining vision (Hayes 2022). It develops postoperatively, most commonly in older individuals and is primarily linked to prior refractive procedures such as LASIK and photorefractive keratectomy ([2]AAO 2024). The pathophysiology involves weakening of the corneal structure following surgery, leaving the cornea vulnerable to outward distension under intraocular pressure. Management options include corneal collagen cross-linking (CXL), visual correction using spectacles, rigid gas permeable contact lenses, intraocular lenses, or intracorneal ring segments (e.g., Intacs, Keraring, Ferrara ring, Myoring) (Hayes 2023). However, many patients experience discomfort or intolerance to rigid lens, and the effectiveness of ring implants may diminish overtime. Corneal collagen cross-linking represents the only treatment shown to directly increase corneal biomechanical strength and slow or halt disease progression, thereby reducing the risk of continued ectasia and delaying or preventing the need for corneal transplantation ([3]AAO 2024; Hayes 2023).

Corneal collagen cross-linking (CXL) is an FDA-approved, in-office procedure used to treat progressive keratoconus and corneal ectasia, with the goal of preserving visual function ([3]AAO 2024). CXL works by strengthening the cornea, slowing or halting the progressive thinning and steepening associated with keratoconus, other corneal diseases, or post-refractive surgery ectasia (Wayman 2024). The procedure induces collagen cross-links within the corneal stroma using a combination of riboflavin (vitamin B2) and ultraviolet A (UVA) light, resulting in increased biomechanical stiffness ([1]AAO 2024; Hayes 2022). CXL can also be combined with other interventions, such as intrastromal corneal ring segments, PRK or phakic intraocular lens implantation, in a strategy referred to as “CXL-plus” (Hayes 2023). These combination therapies aim to enhance visual acuity; however, the evidence supporting improved long-term outcomes beyond corneal stabilization remains limited, and such approaches are considered investigational (Hayes 2023). The two FDA approved methods of CXL are epithelium-off and epithelium-on.

Epithelium-off CXL (“epi-off”) corneal collage cross linking using 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 remains uncertain whether it significantly reduces the long-term need for corneal transplantation. Randomized Controlled Trials (RCTs) have shown that corneal CXL can reduce or even reverse corneal steepening

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in the short term, improving vision. Long-term observational studies demonstrate durable corneal stabilization extending beyond 10 years in the majority of treated eyes, though the degree to which CXL reduces lifetime corneal transplantation risk remains uncertain. Relevant outcome measures include disease progression, functional vision, and procedure-related morbidity. Studies report improvements in corneal thickness and visual maintained over two to three years (Moghadam et al. 2019). Some retrospective studies have indicated positive 10-year outcomes; however, these findings are limited by small sample sizes and incomplete data across patient groups. Larger prospective studies are needed to better assess long-term effectiveness and potential complications.

Epithelium-on CXL ("epi-on") corneal collagen cross-linking using riboflavin 5′-phosphate ophthalmic solutions (Epioxa / Epioxa HD) with ultraviolet A irradiation delivered via an oxygen-enriched light-activation system (O_2n System with Boost Goggles) has been shown to reduce clinical progression of progressive keratoconus. The U.S. Food and Drug Administration approved epithelium-on approach in October 2025, for progressive keratoconus only, based on randomized, sham-controlled clinical trials demonstrating statistically significant stabilization and flattening of maximum keratometry compared with untreated controls. Unlike earlier transepithelial techniques, the FDA-approved epi-on protocol demonstrated statistically significant disease stabilization in randomized, sham-controlled trials. Relevant outcome measures include changes in corneal curvature (Kmax), functional vision, corneal thickness, and procedure-related morbidity. Clinical trial data demonstrate maintenance or modest improvement in visual acuity, stabilization of corneal thickness, and favorable safety and tolerability profiles, with reduced postoperative pain and epithelial healing complications compared with epithelium-off protocols. Follow-up data for FDA-approved epithelium-on CXL are currently limited to short- and intermediate-term outcomes (approximately 12–24 months). While results support effective biomechanical stabilization of keratoconus, long-term durability, retreatment rates, and impact on corneal transplantation rates require further study.

COVERAGE POLICY

NOTE: Photrexa must be utilized as the preferred riboflavin product for corneal collagen cross-linking (CXL) procedures while supplies are available. Use of alternative riboflavin (e.g., Epioxa) products may be considered only when Photrexa is unavailable or unable to be used.

Epithelium-off CXL (Photrexa) 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 the following clinical criteria are met:

1. Member is age 14 years or older

2. Diagnosis of ONE of the following supported by clinical documentation:
    a. Progressive keratoconus (thinning of the cornea)
    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.

3. Member meets ONE of the following according to specific diagnosis:
    a. Progressive Keratoconus
        i. At least ONE of the following changes have occurred within the past 24 months:
            a) Increase of 1.00 diopters (D) or more in the steepest keratometry measurement
            b) Increase of 1.00 D or more in manifest cylinder
            c) Increase of 0.50 D or more in myopia manifest refraction spherical equivalent (MRSE)
        ii. Corrected distance visual acuity worse than 20/20 with properly fitted spectacles or contact lenses
        iii. Corneal thickness ≥ 300 microns
    b. Corneal ectasia resulting from refractive surgery (e.g., LASIK) and ALL the following:
        i. Corrected distance visual acuity worse than 20/20
        ii. Corneal thickness of at least 300 microns at the thinnest area

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4. Requested treatment for ONE of the following. Documentation required:
    a. Left eye
    b. Right eye

5. No history of prior corneal surgery, including intracorneal ring segments

6. Absence of prior ocular herpetic infection

Epithelium-on CXL (Epioxa and Epioxa HD) for the treatment of progressive keratoconus may be **considered medically necessary** when ALL the following clinical criteria are met:

1. Member is age 13 years or older

2. Member meets the following diagnosis criteria for progressive keratoconus:
    a. At least ONE of the following changes have occurred within the past 24 months:
        ii. Increase of 1.00 diopters (D) or more in the steepest keratometry measurement
        iii. Increase of 1.00 D or more in manifest cylinder
        iv. Increase of 0.50 D or more in myopia manifest refraction spherical equivalent (MRSE)
    b. Corrected distance visual acuity worse than 20/20 with properly fitted spectacles or contact lenses
    c. Corneal thickness ≥ 325 microns

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

4. Absence of prior ocular herpetic infection

Limitations and Exclusions

1. Repeat treatment in the same eye is considered **experimental, investigational, and unproven** due to insufficient evidence in the peer-reviewed medical literature to establish long-term safety, efficacy, and effect on net health outcomes.

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

Epithelium-off CXL

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

Epithelium-on CXL

ROUTE OF ADMINISTRATION: Epioxa HD (riboflavin 5'-phosphate ophthalmic solution) 0.239%, for topical ophthalmic use; EPIOXA (riboflavin 5'-phosphate ophthalmic solution) 0.177%, for topical ophthalmic use, for use in conjunction with the O2n System and Boost Goggles

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

FDA-APPROVED USES
Epioxa / Epioxa HD (riboflavin 5′-phosphate ophthalmic solutions) are indicated for use in epithelium-on corneal collagen cross-linking for the treatment of progressive keratoconus in adult and pediatric patients aged 13 years and older, when used in conjunction with the O_2n System and Boost Goggles (FDA 2025).

- **Keratoconus, progressive:** Treatment of progressive keratoconus using an epithelium-on corneal collagen cross-linking protocol with Epioxa / Epioxa HD and the O_2n System with Boost Goggles.
  The FDA issued a new drug application (NDA) approval for Epioxa and Epioxa HD

Refer to the prescribing information for specific dosage and administration instructions. Epioxa and Epioxa HD are only approved for use with the FDA-approved epithelium-on protocol (e.g., Use of the O_2n System and Boost Goggles for oxygen-enriched ultraviolet A [UVA] light delivery).

COMPENDIAL APPROVED OFF-LABELED USES: None

SUMMARY OF MEDICAL EVIDENCE

Epithelium-Off (Photrexa)

The peer-reviewed medical evidence for corneal collagen cross-linking (CXL) for the treatment of keratoconus and corneal ectasia includes randomized controlled trials (RCTs), prospective cohort studies, retrospective comparative analyses, and systematic reviews. Key outcomes reported include disease progression, changes in corneal topography and thickness, visual acuity, and procedure-related adverse events. Collectively, evidence suggests that CXL slows or stops progression of keratoconus and post-refractive ectasia, primarily through topographic flattening of the cornea. The procedure is generally considered safe, with delayed epithelial healing and transient corneal haze being the most frequently reported conditions.

The U.S. Food and Drug Administration (FDA) approved epithelium-off (epi-off) CXL using riboflavin (Photrexa or Photrexa Viscous) and UVA light (KXL system) for the treatment of progressive keratoconus and corneal ectasia following refractive surgery. This approval was supported by three pivotal prospective, open-label, randomized, sham-controlled trials involving a total of 384 patients aged 14 years and older (Table 1). These studies – UVX-001, UVX-

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002, and UVX-003—included patients with either keratoconus or post-refractive surgery ectasia. The trials initially assessed maximum keratometry (Kmax) reduction at 3 months, but this endpoint was later extended to 12 months due to the delayed remodeling response of the corneal stroma post-CXL. Each patient received a single CXL treatment in one eye and was followed for 12 months.

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. Inclusion criteria for these trials required documented progression of keratoconus within the previous 24 months, defined by one or more of the following: a ≥1.0 diopter (D) increase in the steepest keratometry, a ≥1.0 D increase in manifest cylinder, a ≥0.50 D myopic shift in spherical equivalent, or a ≥0.1 mm decrease in the back optical zone radius in rigid contact lens users. Sham eyes received topical anesthetic and riboflavin drops without epithelial debridement or UVA exposure. For sham subjects who crossed over to active treatment at 3 or 6 months, their last pre-treatment Kmax value was carried forward, which likely underestimated the extent of untreated disease progression. At 12 months, Photrexa-treated eyes in UVX-001 showed a mean Kmax reduction of 1.0 D, while sham-treated eyes demonstrated a 1.0 D increase, for a net treatment effect of -2.0 D. In UVX-003, the corresponding figures were a 0.5 D reduction in treated eyes versus a 0.5 D increase in sham eyes, yielding a net effect of -1.1 D. These improvements were correlated with gains in best corrected visual acuity (BCVA). A safety analysis submitted to the FDA included data from 512 treated eyes (293 with keratoconus and 219 with ectasia). Adverse events included corneal haze, epithelial defects, punctate keratitis, striae, pain, dry eye, photophobia, and blurred vision. Most events resolved within 6 months, though corneal opacity persisted at 12 months in up to 6% of ectasia patients.

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

Randomized Controlled Trials

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

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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.

Systematic Reviews and Meta-Analyses
Shajari et al. (2018) completed a meta-analysis of 22 studies comparing conventional CXL (C-CXL) and accelerated CXL (A-CXL) for the treatment of progressive keratoconus. The analysis included 1,158 eyes (577 in the C-CXL group and 581 in the A-CXL group). Primary outcomes included visual acuity, refractive error, corneal thickness, biomechanical properties keratocyte and nerve density, demarcation line depth, and time to re-epithelialization. Both techniques showed similar improvements in uncorrected distance visual acuity (UDVA) through 12 months, after which C-CXL showed greater improvement. C-CXL also showed better correction in spherical error at 3 and 6 months, though A-CXL was superior beyond 6 months. Spherical equivalent and cylindrical error were significantly better with C-CXL at final follow-up. Keratometric changes (Kmax and Kmin) were similar until the final visit, where C-CXL was more effective in flattening the cornea. C-CXL showed greater early reduction in central and minimum corneal thickness, as well as anterior stromal keratocyte density and demarcation line depth. Biomechanical metrics (corneal hysteresis, resistance factor) and nerve density changes were similar between groups. Endothelial cell loss was slightly higher in A-CXL at 1 month, but greater in C-CXL at 6 and 12 months. 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. Overall, both C-CXL and A-CXL were effective, but C-CXL showed superior long-term outcomes in visual acuity and corneal flattening.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence
Moghadam et al. (2019) conducted a prospective interventional study to evaluate the safety and efficacy of corneal collagen cross-linking (CXL) in patients with advanced progressive keratoconus, defined by a maximum keratometry (Kmax) value greater than 58 diopters. The study included 30 eyes from 27 participants, all of whom had a definitive diagnosis warranting CXL. Inclusion criteria included age over 12 years and clinical indication for treatment. Exclusion criteria included pregnancy or lactation, corneal scarring due to advanced keratoconus, and any history of systemic disease, prior corneal or intraocular surgery, chemical ocular injury, delayed epithelial healing, or neurological or retinal disorders affecting vision. Of the 27 participants, 3 underwent bilateral CXL, and 24 received unilateral treatment. Follow-up evaluations were conducted at 1 week, 1, 3-, 6-, 12-, and 24-months post-procedure with Pentacam imaging repeated at 12 and 24 months. The mean UCVA improved from 0.73 ± 0.36 logMAR at baseline to 0.47 ± 0.31 at 12 months and 0.48 ± 0.30 at 24 months. The mean BCVA improved from 0.59 ± 0.34 logMAR to 0.44 ± 0.33 at 12 months and 0.45 ± 0.32 at 24 months. Mean Kmax decreased from 62.19 ± 4.56 D to 60.91 ± 4.36 D at 12 months and 60.95 ± 4.42 D at 24 months. The thinnest point corneal thickness showed only modest changes, from 438.65 ± 40.11 microns at baseline to 430.46 ± 41.05 at 12 months and 431.43 ± 61.92 at 24 months. Results demonstrated meaningful improvements in visual acuity and corneal parameters. Only one eye was classified as a treatment failure, due to a Kmax increase greater than 2.0 D. No intraoperative or postoperative complications were reported. The authors concluded that standard CXL was both safe and effective in stabilizing vision and corneal structure in patients with advanced keratoconus. Limitations of the study included its small sample size, lack of a control group, and nonrandomized design, which may affect generalizability.

Epithelium – On (Epioxa)
The peer-reviewed and regulatory evidence supporting epithelium-on corneal collagen cross-linking (CXL) for the treatment of progressive keratoconus includes randomized, sham-controlled Phase III clinical trials, prospective cohort

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analyses, and regulatory review of pooled efficacy and safety data. Key outcomes evaluated across these studies included disease progression as measured by changes in maximum keratometry (Kmax), visual acuity, corneal thickness, and procedure-related adverse events. Collectively, results demonstrated that FDA-approved epithelium-on CXL protocols are capable of stabilizing progressive keratoconus compared with sham treatment, with a favorable safety and tolerability profile characterized by reduced epithelial morbidity relative to epithelium-off approaches.

The first pivotal Phase III study supporting FDA approval was NCT03442751, a multicenter, randomized, sham-controlled trial evaluating epithelium-on CXL in eyes with progressive keratoconus. Study eyes were randomized in a 2:1 ratio to active treatment or sham control, with the primary efficacy endpoint defined as the between-group difference in mean change in Kmax from baseline at 6 months. The trial demonstrated statistically significant stabilization of corneal curvature in treated eyes compared with continued steepening in sham-treated eyes, meeting its prespecified primary endpoint. Secondary outcomes included assessments of visual acuity and safety, with no serious treatment-related adverse events reported. Procedure-related events were generally mild and transient, including conjunctival hyperemia and temporary corneal opacity.

FDA approval was further supported by a second confirmatory Phase III randomized, sham-controlled trial NCT05759559, designed to replicate and extend the findings of the initial pivotal study and to assess durability of effect through 12 months. This confirmatory trial employed a similar randomized design and evaluated mean change in Kmax as the primary efficacy endpoint, with longer follow-up to account for delayed stromal remodeling associated with CXL. Treated eyes demonstrated statistically significant and clinically meaningful reductions in Kmax compared with sham controls, confirming stabilization of progressive keratoconus. Safety profile remained favorable.

Randomized Controlled Trials
Koppen et al. (2024) conducted a prospective, randomized, controlled, open-label, multicenter trial to evaluate the safety and efficacy of epithelium-on (epi-on) corneal crosslinking (CXL) in patients with keratoconus. The study enrolled 2,228 patients, of which 1,922 (86.3%) had a diagnosis of keratoconus. Subjects were randomized into three treatment groups using different UVA energy protocols, all with the same riboflavin delivery and epi-on technique. Primary outcomes included changes in corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UCVA), and maximum keratometry (Kmax), assessed at 6 and 12 months postoperatively. At 12 months, mean CDVA improved from 20/41 to 20/35 Snellen ($p < 0.001$), and mean UCVA improved from 20/150 to 20/120 Snellen ($p < 0.001$). Kmax decreased by an average of −0.45 D ($p < 0.05$). CDVA remained stable or improved in 80% of patients, increasing to 89% in those ≤21 years. No significant differences in outcomes were found between treatment groups. While Kmax reduction did not correlate directly with visual acuity gains, improved surface regularity was associated with better vision. Corneal thickness remained stable, indicating preserved structural integrity. The treatment was well tolerated, with a low rate of adverse events (8.8%). Epithelial defects occurred in only 1.4% of patients—mostly from one site—and resolved within a week. No serious complications such as corneal striae, infection, or significant haze were observed, offering a safer profile compared to traditional epi-off CXL. Study limitations included the absence of sham control and incomplete 12-month follow-up due to the original 6-month design. The findings support epithelium-on CXL as a safe, noninvasive, and effective treatment for keratoconus.

Iqbal et al. (2020) conducted a prospective, multicentre, randomized controlled trial comparing standard epithelium-off cross-linking (SCXL), accelerated epithelium-off cross-linking (ACXL), and transepithelial epithelium-on cross-linking (TCXL) for progressive pediatric keratoconus. The study's inclusion criteria required patients younger than 18 years with grade 1–3 keratoconus, a minimum corneal thickness >400 µm, and documented progression (Kmax increase >1 D), while exclusion criteria included advanced keratoconus, preoperative corneal opacity, severe dry eye, and any active ocular infection or comorbidity. Outcome criteria consisted of uncorrected and corrected distance visual acuity (UDVA, CDVA), refractive error (sphere, cylinder, spherical equivalent), Kmax, and pachymetry measured preoperatively and at 6, 12, and 24 months. Results showed that SCXL achieved statistically significant improvement across UDVA ($p < 0.0001$), CDVA ($p < 0.0001$ at all points except $p = 0.001$ at month 24), refractive error (sphere $p < 0.0001$; cylinder $p < 0.0001$; spherical equivalent $p < 0.0001$), and Kmax ($p < 0.0001$), with 0% progression at 24 months. ACXL demonstrated early improvements in UDVA ($p = 0.01$ at month 6; $p = 0.007$ at month 12) and CDVA ($p = 0.03$ at month 6; $p = 0.01$ at month 12), but these gains regressed by month 24 (UDVA $p = 0.48$; CDVA $p = 0.09$), and 5.4% progressed by two years. TCXL produced significant deterioration in UDVA and CDVA (UDVA $p = 0.001$ at month 6; $p = 0.02$ at month 12; $p < 0.0001$ at month 24; CDVA $p = 0.001$ at month 6; $p = 0.02$ at month 12; $p < 0.0001$ at month 24), as well as worsening refractive and topographic parameters (sphere $p < 0.0001$ at month 24; cylinder $p = 0.0006$; SE $p < 0.0001$; Kmax $p < 0.0001$), with 28.4% showing progression. Limitations included variation between

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UVA delivery systems and accelerated protocols, bilateral treatment assignments that may introduce intra-subject correlation, and last-observation-carried-forward assumptions for retreated eyes. The authors concluded that SCXL provided the most reliable stabilization and visual/topographic improvement in pediatric keratoconus, ACXL offered moderate but less durable benefit, and TCXL was least effective, with its high failure rate suggesting it should not be the preferred option in this population.

Systematic Reviews and Meta-Analyses

Nughays et al. (2024) conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to compare the efficacy and safety of epithelium-on (epi-on) versus epithelium-off (epi-off) corneal collagen cross-linking (CXL) in patients with corneal ectasia, including keratoconus. Inclusion criteria consisted of English-language RCTs enrolling patients with any form of corneal ectasia that directly compared epi-on and epi-off CXL techniques, while exclusion criteria included non-comparative studies, non-ectatic corneal conditions, non-randomized designs, and studies that did not report clinically relevant outcomes. Outcome criteria focused on the change in maximal keratometry (Kmax) at 12 months as the primary endpoint, with secondary outcomes including best-corrected and uncorrected visual acuity (BCVA and UCVA), spherical equivalent (SE), endothelial cell count (ECC), corneal curvature parameters, and treatment-related adverse events. Thirteen RCTs comprising 872 patients and 1041 eyes met inclusion criteria, with quantitative meta-analysis demonstrating no statistically significant differences between epi-on and epi-off CXL for Kmax ($p = 0.76$), BCVA ($p = 0.48$), UCVA ($p = 0.49$), or spherical equivalent, while heterogeneity ranged from low to high depending on the outcome (I^2 0–91%). Epi-off CXL was associated with significantly greater endothelial cell loss ($p < 0.01$) and a higher incidence of adverse events, including corneal haze, delayed epithelial healing, pain, and postoperative discomfort, whereas epi-on CXL demonstrated a more favorable safety profile with fewer complications. Limitations included heterogeneity in patient populations, variability in riboflavin formulations, UVA fluence and accelerated protocols, limited pediatric representation, small sample sizes within individual trials, and follow-up largely restricted to 12 months. The authors concluded that epi-on and epi-off CXL provide comparable short-term efficacy in stabilizing corneal ectasia, but epi-on CXL offers improved safety and tolerability, underscoring the importance of individualized treatment selection based on patient risk profile, corneal characteristics, and tolerance for procedure-related morbidity.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Halašová et al. (2026) reported a prospective, observational, single-center comparative study evaluating epithelium-on customized remodeled vision (CuRV) cross-linking versus epithelium-off accelerated corneal cross-linking (aCXL) for the treatment of progressive keratoconus over a 24-month follow-up period. Inclusion criteria consisted of adult eyes with progressive keratoconus classified as Krumeich-Amsler grades 1 to 3–4, corneal thickness ≥400 µm, and endothelial cell density ≥1500 cells/mm², while exclusion criteria included prior corneal surgery, corneal scarring or dystrophies, pellucid marginal degeneration, systemic connective tissue disease, uncontrolled diabetes, pregnancy or breastfeeding, and other ocular comorbidities. Outcome measures included changes in uncorrected and corrected distance visual acuity, manifest refraction spherical equivalent, maximum and mean keratometry (Kmax, Kmean), keratometric meridians, thinnest corneal thickness, higher-order aberrations, endothelial cell density, and treatment-related adverse events. Results from 179 eyes (135 patients) showed that the CuRV group achieved significantly greater and sustained corneal flattening than the aCXL group at 2 years, with larger reductions in Kmax ($p = 0.0018$) and Kmean ($p = 0.0367$), as well as a lower rate of postoperative Kmax progression >1 D (1% vs 9%). Improvements in higher-order aberrations occurred in both groups but were significantly greater in the CuRV cohort ($p < 0.0001$), accompanied by greater gains in visual acuity and refractive stability. Safety outcomes indicated no significant endothelial cell loss in either group and no severe complications, although transient stromal haze occurred more frequently and persisted longer in the aCXL group. Limitations of the study included its nonrandomized design, single-center setting, baseline differences in corneal steepness between groups, and reliance on a single experienced surgeon for individualized treatment planning, which may limit generalizability. The authors concluded that the epithelium-on CuRV protocol provides effective and durable stabilization of keratoconus with superior corneal regularization and visual outcomes compared with epithelium-off accelerated CXL, while offering potential advantages in postoperative comfort, safety, and recovery.

Henríquez et al. (2017) conducted a prospective, nonrandomized cohort study comparing accelerated transepithelial epithelium-on corneal collagen cross-linking (A-epi-on CXL) with standard epithelium-off CXL in pediatric patients with progressive keratoconus. Outcome measures included changes in uncorrected and best-corrected visual acuity, maximum keratometry (Kmax), pachymetry, posterior corneal elevation, and rates of keratoconus progression assessed preoperatively and at 6 and 12 months post-procedure using Scheimpflug imaging. Results from 61 eyes

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(51 patients) demonstrated modest improvements in uncorrected visual acuity in both groups that were not statistically significant (A-epi-on $p = 0.09$; epi-off $p = 0.16$), while best-corrected visual acuity improved significantly at 12 months in both groups (A-epi-on $p = 0.05$; epi-off $p = 0.05$). Mean Kmax changes at 12 months were +0.1 diopters (D) in the A-epi-on group ($p = 0.62$) and −0.94 D in the epi-off group ($p = 0.11$), with no statistically significant between-group differences for pachymetry or posterior elevation parameters ($p > 0.05$). Keratoconus progression occurred in 5.6% of eyes treated with accelerated epi-on CXL and 12% of eyes treated with standard epi-off CXL during the 12-month follow-up period. Limitations of the study include its nonrandomized design, small sample size, short duration of follow-up, and limited power to detect differences in keratometric outcomes or progression rates. The authors concluded that both accelerated epi-on and standard epi-off CXL appeared safe and effective in halting short-term progression of pediatric keratoconus at one year, while acknowledging the need for longer-term data to assess durability of treatment effects.

Henríquez et al. (2020) reported the five-year follow-up outcomes of the pediatric cohort previously treated with accelerated epithelium-on and standard epithelium-off corneal collagen cross-linking, providing insight into long-term durability and disease control. Results from 78 eyes demonstrated statistically significant improvement in BCVA in both groups at five years (A-epi-on $p = 0.03$; epi-off $p < 0.001$); however, the epi-off group showed substantially greater and more sustained corneal flattening, with a mean reduction in keratometry of 3.18 diopters compared with 0.09 diopters in the A-epi-on group ($p < 0.001$). Significant between-group differences favoring epi-off CXL were also observed for cylinder reduction, flat and mean keratometry, and pachymetry (all $p < 0.05$). Keratoconus progression occurred in 9.37% of eyes treated with accelerated epi-on CXL, while no progression was observed in the epi-off group at five years. Limitations of the long-term analysis include the nonrandomized design, single-center experience, and limited sample size. Overall, the five-year data suggest that while both approaches may provide short-term stabilization, epithelium-off CXL offers superior long-term biomechanical stability and disease control in pediatric patients with progressive keratoconus.

National and Specialty Organizations

The **American Academy of Ophthalmology (AAO)** published a Preferred Practice Pattern pertaining to corneal ectasia in 2024 ([2]AAO 2024), reaffirming CXL as the only intervention demonstrated to slow or halt progression of keratoconus and post-refractive corneal ectasia. The AAO recommends CXL for patients with documented progression, particularly in mild to moderate disease, and emphasizes early intervention to preserve visual function and reduce the likelihood of corneal transplantation. While epithelium-off CXL is recognized as the historical standard with the most extensive long-term data, the AAO acknowledges emerging evidence supporting FDA-approved epithelium-on CXL protocols that utilize enhanced riboflavin permeability and oxygen-enriched ultraviolet A delivery. The AAO notes that these newer epithelium-on approaches offer improved postoperative comfort and safety profiles, with short- to intermediate-term outcomes demonstrating effective disease stabilization when used in appropriately selected patients. The AAO further emphasizes the importance of individualized patient selection, adherence to device-specific FDA labeling, and continued longitudinal monitoring following treatment.

The **American Society of Cataract and Refractive Surgery (ASCRS)**, through its Cornea Clinical Committee, published a comprehensive evidence-based review on corneal collagen cross-linking that has been reaffirmed in subsequent updates (Beckman et al. 2019). ASCRS concluded that epithelium-off CXL remains the reference standard for biomechanical strengthening of the cornea, with strong evidence supporting durable stabilization of progressive keratoconus and a reduction in the need for corneal transplantation. The Society recognizes that advances in riboflavin formulations, ultraviolet light delivery, and oxygen kinetics have led to the development of FDA-approved epithelium-on CXL protocols, which demonstrate clinically meaningful stabilization with improved tolerability and reduced epithelial morbidity. ASCRS supports the use of FDA-approved CXL techniques within their labeled indications and underscores that differences in efficacy, depth of cross-linking, and long-term durability should be considered when selecting between epithelium-off and epithelium-on approaches. Ongoing research and long-term comparative data are encouraged to further refine patient selection and optimize outcomes.

SUPPLEMENTAL INFORMATION

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

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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)

Code	Description
0402T	Collagen cross-linking of cornea, including removal of the corneal epithelium, when performed, and intraoperative pachymetry, when performed

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
J2787	Riboflavin 5'-phosphate, ophthalmic solution (Photrexa Viscous/Photrexa), up to 3 ml
J2789	Riboflavin 5'-phosphate, ophthalmic solution (Epioxa HD/Epioxa), up to 2 ml

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

08/12/2026	Policy revised. Changed coverage stance pertaining to Epioxa from experimental/investigation/unproven to medically necessary. Added note to utilize Photrexa over Epioxa until supplies run out.
04/08/2026	Policy revised. Updated coverage criteria to address Epithelium-On corneal collagen cross linking as E/I/U. Updated Summary of Medical Evidence and References. IRO Peer Review on April 1, 2026, by a practicing physician board-certified in Ophthalmology.
08/13/2025	Policy revised. Removed prescriber requirements. Updated Summary of Medical Evidence and References. IRO Peer Review on July 11, 2025, by a practicing physician board-certified in Ophthalmology.
08/14/2024	Policy reviewed, no changes to criteria. Updated References.
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.
07/2020	Policy re-instated. 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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