

Corneal Collagen Cross-Linking

MEDICAL POLICY NUMBER: 158

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**INSTRUCTIONS FOR USE:** Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

**SCOPE:** Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

## PLAN PRODUCT AND BENEFIT APPLICATION

☒ Commercial

☒ Medicaid/OHP\*

☐ Medicare\*\*

### \*Medicaid/OHP Members

*Oregon:* Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

Corneal Collagen Cross Linking: Guideline Note 9

### \*\*Medicare Members

This Company policy may be applied to Medicare Plan members only when directed by a separate Medicare policy. Note that investigational services are considered “**not medically necessary**” for Medicare members.

## COVERAGE CRITERIA

- I. Conventional, epithelium-off, corneal collagen cross-linking (C-CXL) using an FDA-approved system may be considered **medically necessary** for the treatment of **progressive** keratoconus when **all** of the following criteria are met (A. – E.):
  - A. Age between 14 and 65 years; **and**
  - B. Diagnosis of keratoconus based on keratometry and corneal mapping; **and**
  - C. Corrected distance visual acuity (CDVA) worse than 20/20, **and**
  - D. Documentation indicates that any of the following changes have occurred:
    1. Increase of 1.00 diopters (D) or more in the steepest keratometry (K) measurement, **or**
    2. Increase of 1.00 D or more in manifest cylinder, **or**
    3. Increase of 0.50 D or more in manifest refraction spherical equivalent (MRSE); **or**
    4. A 1.0 D or a 0.1 mm or more decrease in the back optic zone radius of contact lens wearers, where other information is not available; **and**
  - E. No history of corneal or systemic disease that may interfere with healing after the procedure, including but not limited to any of the following:
    1. Chemical injury or burns
    2. Delayed epithelial healing
    3. Severe infections
    4. Other corneal or ocular surface disorders
- II. Conventional, epithelium-off, corneal collagen cross-linking (C-CXL) using an FDA-approved

system may be considered **medically necessary** for the treatment of corneal ectasia resulting from refractory surgery when **all** of the following criteria are met (A. – E.):

- A. Conservative treatment has failed (e.g., spectacle correction, rigid contact lens); **and**
- B. Age between 14 and 65 years; **and**
- C. Axial topography pattern consistent with corneal ectasia; **and**
- D. Corrected distance visual acuity (CDVA) worse than 20/20, **and**
- E. No history of corneal or systemic disease that may interfere with healing after the procedure, including but not limited to any of the following (1.-5.):
  - 1. Chemical injury or burns
  - 2. Delayed epithelial healing
  - 3. Severe infections
  - 4. Other corneal or ocular surface disorders
  - 5. Prior corneal surgery other than refractive surgery

III. Collagen cross-linking is considered **not medically necessary** when criterion I above is not met, including but not limited to:

- A. The use of other CXL techniques and protocols, including but not limited to:
  - 1. Transepithelial collagen cross-linking (Epithelium-on, T-CXL).
  - 2. Accelerated CXL (A-CXL).
  - 3. Partial epithelium-removal CXL (P-CXL).
  - 4. Topography-guided CXL (TG-CXL).
- B. When CXL is used in combination with other procedures, also known as CXL-plus (e.g., intrastromal corneal ring segments, PRK or phakic intra-ocular lens implantation).
- C. Treatment of other corneal indications, including, but not limited to infectious keratitis.

Link to [Evidence Summary](#)

## POLICY CROSS REFERENCES

None

The full Company portfolio of current Medical Policies is available online and can be [accessed here](#).

## POLICY GUIDELINES

### DOCUMENTATION REQUIREMENTS

The following information must be submitted in order to determine if medically necessity criteria are met:

- Keratometry and corneal mapping, **and**
- Documentation of corrected distance visual acuity and refraction, current and prior results showing change

## BACKGROUND

### Corneal Collagen Cross-Linking (CXL)

Corneal collagen cross-linking (CXL), also simply known as corneal cross-linking, is a relatively new technique currently being investigated as a treatment to slow the progression of corneal ectasias, including keratoconus and postkeratorefractive ectasia, as well as other corneal conditions.

CXL is thought to increase the biomechanical strength of collagen fibrils of the cornea through the application of riboflavin (vitamin B2) eye drops, which are absorbed by the corneal stroma. After the application of the drops, ultraviolet A (UVA) radiation is used to trigger a photochemical reaction that changes the cross-links between and within collagen fibers in the stroma. This is believed to strengthen and increase the biomechanical stiffness of the stroma, thereby flattening the steepened cornea into a more normal shape to improve vision.

Different approaches to remove or penetrate the corneal epithelium and different UVA light intensities have given rise to a variety of CXL approaches:

- *Conventional CXL (C-CXL), also known as “epithelium off”*: C-CXL involves removing the epithelium completely, after which riboflavin drops are applied to the cornea and the UVA irradiation is administered for 30 minutes.
- *Accelerated CXL (A-CXL)*: A-CXL administers a similar UVA dose (fluence) to C-CXL, but in a shorter amount of time (10 minutes) by increasing the fluence rate or irradiance.
- *Transepithelial CXL (T-CXL), also known as “epithelium on”*: T-CXL is performed without epithelial removal in an effort to reduce patient discomfort and possibly lower the risk of infection compared with C-CXL. However, reduced absorption of riboflavin has been reported in the T-CXL approach.
- *Partial Epithelium-Removal CXL (P-CXL)*: P-CXL is performed by partially removing the epithelium in an effort to reduce corneal damage and promote faster reepithelialization. However, as with T-CXL, reduced riboflavin absorption has been reported.
- *Topography-Guided CXL (TG-CXL)*: TG-CXL is performed using a customized, patient-specific UVA irradiation pattern based on circular zones over the keratoconic cone region of the cornea. These zones are centered on the maximum posterior elevation and receive varying amounts of energy depending on the severity of the curvature, with higher levels of energy being delivered to the innermost zones compared with outmost zones.
- *CXL combined with other procedures (CXL-plus)*: CXL-plus is the term used when either C-CXL or T-CXL are combined with other interventions, including but not limited to intrastromal corneal ring segments, photorefractive keratectomy (PRK) or phakic intra-ocular lens implantation.

### Corneal Ectasia

According to the American Academy of Ophthalmology (AAO), “corneal ectasia is a noninflammatory condition, the hallmark of which is progressive corneal steepening and thinning.”<sup>1</sup> As a result, the cornea bulges outward and progressively develops a conical shape, which prevents light entering the eye from

focusing directly on the retina, resulting in irregular astigmatism and progressive myopia or visual loss. “Corneal ectasias are associated with decreased uncorrected visual acuity (UCVA), an increase in ocular aberrations, and often a loss of best-corrected distance visual acuity (BCVA). Corneal ectasias can result in significant ocular morbidity and may require surgical intervention. Types of corneal ectasia include keratoconus, postkeratorefractive ectasia, pellucid marginal degeneration, keratoglobus, and wound ectasia after penetrating keratoplasty (PK).”

The clinical objectives for treating corneal ectasia are to understand appropriate surgical and non-surgical treatment options and to improve and/or prevent loss of visual function.

### Alternative Treatment Options

Apart from CXL, alternative treatment options for corneal ectasias include corrective lenses, gas-permeable contact lenses, and intraocular lenses. However, many patients cannot tolerate the rigid lenses. Alternatively, minimally invasive intracorneal ring segment implantation (e.g., Intacs, Keraring, Ferrara ring, Myoring) is another treatment option. However, the initial effects of the rings are reported to regress with time. Ablative procedures including photorefractive keratectomy, phototherapy keratectomy, lamellar keratoplasty, and penetrating keratoplasty are also an option. However, none of these treatments change the course of the disease, and patients with advanced disease often need corneal transplantation.

### **Keratoconus**

Keratoconus is the most common corneal ectasia, with prevalence reporting between estimates 760 to 3300 cases per 100,000 people. Naturally occurring keratoconus typically begins in the second decade of life and progresses until about age 40. It is a predominantly bilateral form of corneal degeneration but may be asymmetrical as well. In keratoconus, collagen fibers within the cornea naturally weaken and the cornea can no longer maintain the normal round shape, causing loss of visual acuity.

### **Postkeratorefractive Ectasia**

Postkeratorefractive ectasia, also known as keratectasia, is a type of secondary corneal ectasia that has been associated with refractive surgery, particularly laser-assisted in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK). The incidence is rare, with between 0.02% and 0.6% of LASIK patients developing the condition. Postkeratorefractive ectasia may occur within a week of surgery or several years later, but the majority of cases occur within two years post-LASIK. Although it has not been clearly established, post-surgery ectasia is hypothesized to develop in patients whose cornea is already weak and predisposed to ectasia. Conversely, it may occur when a normal cornea is weakened by surgery to a point of instability.

## **REGULATORY STATUS**

### **U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

In 2016, PHOTREXA® VISCOUS and PHOTREXA® were approved and are indicated for use in corneal collagen cross-linking in combination with the KXL™ System (NDA #203324) for the treatment of progressive keratoconus and corneal ectasia following refractive surgery.<sup>2</sup>

PHOTREXA® is a 0.146% riboflavin 5'-phosphate ophthalmic solution), while PHOTREXA® VISCOUS is a 0.146% riboflavin 5'-phosphate in 20% dextran ophthalmic solution. Both solutions are for topical ophthalmic use and are only approved for use with the Avedro with the KXL™ System, which is the company's specific UVA irradiation device.

The Dosage and Administration" section of the FDA label indicates usage only of the conventional "epithelium-off" CXL protocol (C-CXL). 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).

## **CLINICAL EVIDENCE AND LITERATURE REVIEW**

### **EVIDENCE REVIEW**

Currently, the only corneal collagen cross-linking (CXL) system with FDA approval is the KXL® System (Avedro). The KXL® System is only indicated for use with the conventional "epithelium-off" C-CXL protocol and only as a treatment for keratoconus or corneal ectasia following refractive surgery. The KXL® System is not approved for use with any other CXL technique or protocol, including but not limited to:

- Transepithelial collagen cross-linking (Epithelium-on, T-CXL)
- Accelerated CXL (A-CXL)
- Partial epithelium-removal CXL (P-CXL)
- Topography-guided CXL (TG-CXL)
- CXL combined with another procedure (CXL-plus)

The health plan considers devices that are not FDA-approved to be not medically necessary. The following evidence review is only focused on FDA-approved devices. In addition, evidence reviews for indications not covered by the FDA (e.g., infectious keratitis) were conducted at this time.

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of conventional corneal collagen cross-linking (C-CXL) as a treatment for keratoconus or corneal ectasia following refractive surgery. Below is a summary of the available evidence identified through May 2024.

### **Keratoconus**

#### Systematic Reviews

In 2019, ECRI published a rapid response review of CXL for treating keratoconus and corneal ectasia, which was last updated in February 2019.<sup>3</sup> Given the large body of evidence, ECRI included systematic reviews (SRs) with meta-analysis and randomized controlled trials (RCTs) with 30 or greater patients in their review. Included studies assessed 2,000+ eyes. Overall, ECRI reports the evidence is favorable based on one recent SR and three RCTs not included in the SR, which found CXL-treated patients had improved visual acuity one year after treatment. Adverse event reports have been low. Long term data are still lacking; the ECRI authors concluded that longer term RCTs are still warranted.

In recent years, a large number of systematic reviews have been published on the efficacy of C-CXL for the treatment of keratoconus. The summary of the reviews below is organized by comparator group.

Two systematic reviews have assessed the efficacy of CXL for the treatment of keratoconus without specifically comparing it to another treatment. These reviews included large numbers of randomized and nonrandomized studies and have reported one or more of the following significant improvements among patients treated with C-CXL:<sup>4,5</sup>

- improved visual acuity, as measured by uncorrected distance visual acuity (UDVA) and/or best-spectacle-corrected visual acuity (BSCVA)
- improved topography parameters:
  - reduced central corneal thickness (CCT)
  - improved refractive cylinder
  - improvements in other topography readings
- decreased endothelial cell density

In addition, in 2016, McAnena et al. published a systematic review that evaluated C-CXL in pediatric patients (aged 18 years or younger), including nine studies.<sup>6</sup> The review reported improved UDVA and BSCVA and stable corneal curvature (as measured by maximum keratometry [Kmax]) at one-year post-procedure. They concluded that C-CXL may be effective in halting progression of keratoconus in pediatric patients.

Two meta-analyses and a Cochrane review analyzed a total of five RCTs comparing C-CXL versus no treatment, and reported one or more of the following significant improvements among patients treated with C-CXL compared with untreated eyes:<sup>7-9</sup>

- improved corrected visual acuity, as measured by BSCVA
- improved topography parameters: reduced corneal curvature, as measured by a decrease in maximum keratometry (Kmax)

Four meta-analyses have compared C-CXL with modified CXL techniques (A-CXL or T-CXL) and reported one or more of the following significant improvements among patients treated with C-CXL compared with modified techniques:<sup>10-13</sup>

- reduced corneal curvature (Kmax)
- delayed deterioration of Kmax
- improved minimum keratometry (minK)
- greater reduction in mean keratometry (mean K)
- improved demarcation line depth

In 2022, Hayes published an updated comparative effectiveness review of CXL for treatment of keratoconus.<sup>14</sup> The review of twenty-three studies included nine RCTs, two prospective trials with historical controls, six prospective comparative cohort studies, and six retrospective comparative cohort studies. Despite the “C” rating given to the use of C-CXL for the treatment of progressive keratoconus in adolescent and adult patients, the review did note that there is a moderately sized body of low-quality evidence that suggested that C-CXL may slow or stop progression of keratoconus when compared to no treatment or sham treatment. Hayes noted that it is unclear how visual acuity and corneal thickness outcomes are affected by CXL as most studies were relatively small, with immediate follow-up durations (1-3 years).

## **Corneal Ectasia Following Refractive Surgery**

### Systematic Reviews

In 2017, a systematic review was published that assessed the efficacy of CXL for the treatment of post-laser vision correction ectasia, including seven studies (118 patients, 140 eyes) treated with CXL for progressive ectasia after laser-assisted in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK).<sup>15</sup> The follow-up time ranged from 12 to 62 months and the review reported significantly improved corrected distant visual acuity (CDVA) in patients who underwent CXL. Of note, the five RCTs included in the review were all small in sample size and conducted on patient cohorts outside of the United States.

### Randomized Controlled Trials

Outside of the United States there have been a number of RCTs published by the same group, using the same patient population, simply reporting various one-year outcomes of CXL for the treatment of corneal ectasia after previous refractive surgery.<sup>16-19</sup> Collectively, these publications reported significant improvements in the following:

- corneal topography, including improvements in the index of surface variance, index of vertical asymmetry, keratoconus index, and minimum radius of curvature.
- improved visual acuity measures, including UDVA and CDVA.

This same group (Hersh et al. 2017) published the results of their first U.S. trial, the pivotal trial that was used as the basis for the FDA approval of the Avedro KXL System for this indication.<sup>20</sup> The authors published one-year results of the prospective multicenter RCT, including 179 patients randomized to either standard C-CXL or a sham control where riboflavin drops were applied without removal of the epithelium.<sup>20</sup> In the C-CXL treatment group, Kmax decreased by 0.7 diopters (D) from baseline to one-year, whereas there was continued progression of corneal steepening in the control group (1.3 D difference between treatment and control,  $P < 0.0001$ ). In the treatment group, the Kmax value decreased by 2.0 D or more in 14 eyes (18%) and increased by 2.0 D or more in three eyes (4%). Both the CDVA and the UDVA improved significantly in the C-CXL group. The authors concluded the C-CXL “was effective in improving the maximum K value, CDVA, and UDVA in eyes with corneal ectasia one year after treatment, with an excellent safety profile.”

## **CLINICAL PRACTICE GUIDELINES**

### **American Academy of Ophthalmology (AAO)**



In 2024, the AAO published an updated Preferred Practice Guideline pertaining to corneal ectasia.<sup>21</sup> In the highlights and recommendations for care, the AAO stated that CXL, “reduces the risk of progressive ectasia in patients with keratoconus. It also stabilizes cases of corneal ectasia occurring after keratorefractive surgery but is generally not as effective in this later setting.” The guideline includes an extensive section on corneal cross-linking with indications, technique options, outcomes, contraindications, complications, and varying combination techniques.

### **National Institute for Health and Care Excellence (NICE)**

In 2013, NICE published an interventional procedures guidance on photochemical corneal collagen cross-linkage using riboflavin and UVA for keratoconus and keratectasia.<sup>22</sup> NICE noted that the majority of evidence focused on the epithelium-off (C-CXL) approach as a treatment for keratoconus and corneal ectasia. Transepithelial CXL (T-CXL, epithelium-on) procedure had considerably less evidence. In addition, “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.”

The NICE guidance recommended the following:

- “Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia is adequate in quality and quantity.
- Current evidence on the safety and efficacy of epithelium-on (transepithelial) CXL, and the combination (CXL-plus) procedures for keratoconus and keratectasia is inadequate in quantity and quality.
- Patient selection for these procedures should include assessment of corneal thickness and consideration of the likelihood of disease progression.
- The procedures should only be carried out by ophthalmologists with expertise in managing corneal disease and specific training in the use of UV light or by appropriately trained staff under their supervision.”

### **EVIDENCE SUMMARY**

There is enough evidence to show that conventional epithelium-off corneal collagen cross-linking (C-CXL) for the treatment of keratoconus and post-laser vision correction ectasia may improve overall health outcomes in highly selective patient populations. The current research has limitations, including a small number of studies reporting long-term follow-up. However, C-CXL appears to improve visual acuity and corneal curvature for a moderate amount of time (one- to three- years), thereby postponing corneal transplantation. Current guidelines based on research recommend the use of C-CXL for keratoconus and post-laser vision correction ectasia. Therefore, C-CXL for keratoconus and post-laser vision correction ectasia may be considered medically necessary and covered when policy criteria are met. Due to a lack of evidence and clinical practice guidelines, C-CXL and other CXL protocols (e.g. T-CXL, A-CXL, CXL-plus) not approved by the FDA are considered not medically necessary and not covered when policy criteria are not met.

## HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism. The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online [here](#).

## BILLING GUIDELINES AND CODING

Corneal collagen cross-linking (CXL) maybe be requested in combination with other procedures, such as phototherapeutic keratectomy (PTK). These combination procedures are considered investigational per this medical policy. Therefore, when the HCPCS code for PTK (S0812) is billed with 0402T, both codes should deny as investigational.

CODES*		
CPT	0402T	Collagen cross-linking of cornea, (including removal of the corneal epithelium and intraoperative pachymetry, when performed) (Report medication separately)
	66999	Unlisted procedure, anterior segment of eye
HCPCS	J2787	Riboflavin 5'-phosphate, ophthalmic solution, up to 3 mL

### \*Coding Notes:

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- See the non-covered and prior authorization lists on the Company [Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website](#) for additional information.

- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as “medically unlikely edits” (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

## REFERENCES

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## POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
9/2023	Annual update. Changed denial language from investigational to not medically necessary.
7/2024	Annual review. No changes.
7/2025	Annual review. No changes.