Introduction

The cornea is the outermost layer of the eye. It’s clear and shaped like a dome. Besides keeping dirt and germs out of the eye, the cornea is important for focused vision. This is because the cornea bends (refracts) light as it comes into the eye. If the curvature of the cornea is distorted, the eye’s focus also is distorted. Certain diseases or injuries change the shape of the cornea. Progressive keratoconus is a condition in which the cornea bulges outward into a cone shape. Corneal ectasia is a condition in which the inner layers of the cornea become weak, allowing the cornea to press forward. Distorted vision caused by these two conditions can often be corrected by eyeglasses or rigid contact lenses. Another treatment calls for vitamin B2 (riboflavin) to be placed in the eye, followed by the use of ultraviolet A light. This is known as corneal cross-linking. The goal of this treatment is to make the corneal tissues stronger. This policy discusses when corneal cross-linking is considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Note: Refer to member contract for benefit determination on coverage of LASIK refractive surgery when applicable.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Corneal collagen cross-linking | Corneal collagen cross-linking using riboflavin (eg, Photorexa®) and ultraviolet A may be considered medically necessary in patients who have failed conservative treatment (eg spectacle correction, rigid contact lens) as a treatment of:  
  • Progressive keratoconus (thinning of the cornea)  
  OR  
  • Corneal ectasia (corneal thinning and protrusion) after refractive surgery (eg, LASIK or photorefractive keratectomy [PRK]) |

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal collagen cross-linking</td>
<td>Corneal collagen cross-linking using riboflavin and ultraviolet A is considered investigational for all other indications.</td>
</tr>
</tbody>
</table>

Documentation Requirements
The patient’s medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:
• Failure of conservative treatment (eg spectacle correction, rigid contact lens) to treat:
  o Progressive keratoconus (thinning of the cornea)
  OR  
  o Corneal ectasia (corneal thinning and protrusion) after refractive surgery (eg, LASIK or photorefractive keratectomy [PRK])

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT</td>
<td></td>
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<tr>
<td>0402T</td>
<td>Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed)</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>J2787</td>
<td>Riboflavin 5'-phosphate, ophthalmic solution, up to 3 mL (new code effective 1/1/19)</td>
</tr>
<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
</tr>
</tbody>
</table>

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

**Related Information**

Progressive keratoconus or corneal ectasia is defined as one or more of the following:

- An increase of 1 diopter (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.

**Evidence Review**

**Description**

Corneal collagen cross-linking (CXL) is a photochemical procedure approved by the Food and Drug Administration for the treatment of progressive keratoconus and corneal ectasia. Keratoconus is a dystrophy of the cornea characterized by progressive deformation (steepening) of the cornea while corneal ectasia is keratoconus that occurs after refractive surgery. Both lead to functional loss of vision and need for corneal transplantation.
Background

*Keratoconus and Ectasia*

Keratoconus is a bilateral dystrophy characterized by progressive ectasia (paracentral steepening and stromal thinning) that impairs visual acuity. While frequently diagnosed at a young age, the progression of keratoconus is variable. Results from a longitudinal study with 7 years of follow-up showed that, over the study period, there was a decrease of 2 high- and 4 low-contrast letters in best-corrected visual acuity.\(^2\) About 1 in 5 patients showed a decrease of 10 or more letters in high-contrast visual acuity and one-third of patients showed a decrease of 10 or more letters in low-contrast visual acuity. Over 8 years of follow-up, there was a mean increase of 1.44 diopters (D) in First Definite Apical Clearance Lens (a rigid contact lens to measure corneal curvature) and 1.6 D in flatter keratometric reading.

Ectasia (also known as keratectasia, iatrogenic keratoconus, or secondary keratoconus) is a serious long-term complication of laser in situ keratomileusis surgery and photorefractive keratectomy. It is similar to keratoconus but occurs postoperatively and primarily affects older populations. It may result from unrecognized preoperative keratoconus or, less frequently, from the surgery itself. Similar to keratoconus, it is characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of visual acuity.

Treatment

The initial treatment for keratoconus often consists of hard contact lenses. A variety of keratorefractive procedures have also been attempted, broadly divided into subtractive and additive techniques. Subtractive techniques include photorefractive keratectomy or laser in situ keratomileusis, although generally, results of these techniques have been poor. Implantation of intrastromal corneal ring segments is an additive technique in which the implants are intended to reinforce the cornea, prevent further deterioration, and potentially obviate the need for penetrating keratoplasty. Penetrating keratoplasty (ie, corneal grafting) is the last line of treatment. About 20% of patients with keratoconus will require corneal transplantation. All of these treatments attempt to improve the refractive errors but are not disease-modifying.

Treatment options for ectasia include intraocular pressure-lowering drugs and intracorneal ring segments. Frequently, penetrating keratoplasty is required.

None of the currently available treatment options for keratoconus and corneal ectasia halt the progression of the disease, and corneal transplantation is the only option available when functional vision can no longer be achieved.
Corneal collagen cross-linking (CXL) has the potential to slow the progression of the disease. It is performed with the photosensitizer riboflavin (vitamin B₂) and ultraviolet A irradiation. There are 2 protocols for CXL.

1. Epithelium-off CXL (also known as “epi-off”): In this method, about 8 mm of the central corneal epithelium is removed under topical anesthesia to allow better diffusion of the photosensitizer riboflavin into the stroma. Following de-epithelialization, a solution with riboflavin is applied to the cornea (every 1-3 minutes for 30 minutes) until the stroma is completely penetrated. The cornea is then irradiated for 30 minutes with ultraviolet A 370 nm, a maximal wavelength for absorption by riboflavin, while the riboflavin continues to be applied. The interaction of riboflavin and ultraviolet A causes the formation of reactive oxygen species, leading to additional covalent bonds (cross-linking) between collagen molecules, resulting in stiffening of the cornea. Theoretically, by using a homogeneous light source and absorption by riboflavin, the structures beyond a 400-μm thick stroma (endothelium, anterior chamber, iris, lens, retina) are not exposed to an ultraviolet dose that is above the cytotoxic threshold.

2. Epithelium-on CXL (also known as “epi-on” or transepithelial): In this method, the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed.

Currently, the only CXL treatment approved by the Food and Drug Administration is the epithelium-off method. There are no Food and Drug Administration–approved CXL treatments using the epithelium-on method. CXL is being evaluated primarily for corneal stabilization in patients with progressive corneal thinning, such as keratoconus and corneal ectasia following refractive surgery. CXL may also have anti-edematous and antimicrobial properties.

**Summary of Evidence**

For individuals who have progressive keratoconus who receive CXL using riboflavin and ultraviolet A, the evidence includes multiple RCTs, systematic reviews, and nonrandomized studies. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. In both pivotal RCTs, the primary end point (an intermediate outcome) of reducing maximum corneal curvature (Kmax) by 1 D was achieved at month 3 and maintained at months 6 and 12 in CXL-treated patients compared with sham controls. In both RCTs, the difference in mean change in Kmax from baseline to 12 months was 1.9 D and 2.3 D, respectively, favoring the CXL-treated patients. Long-term follow-up for visual acuity outcomes are needed. The adverse events associated with CXL include corneal opacity (haze), corneal
epithelial defects, and other ocular findings. Most adverse events resolved in the first month but
continued in a few (1%-6%) patients for 6 to 12 months. The evidence is sufficient to determine
that the technology results in a meaningful improvement in the net health outcome.

For individuals who have corneal ectasia after refractive surgery who receive CXL using riboflavin
and ultraviolet A, the evidence includes multiple RCTs, systematic reviews, and nonrandomized
studies. Relevant outcomes are change in disease status, functional outcomes, and treatment-
related morbidity. In both pivotal RCTs, the primary end point (an intermediate outcome) of
reducing Kmax by 1 D was achieved at month 3 and maintained at months 6 and 12 in the CXL-
treated patients compared with sham controls. In both RCTs, the difference in mean change in
Kmax from baseline to 12 months was 2.0 D and 1.1 D, respectively, favoring CXL-treated
patients. Long-term follow-up for visual acuity outcomes are needed. The adverse events
associated with CXL include corneal opacity (haze), corneal epithelial defects, and other ocular
findings. Most adverse events resolved in the first month but continued in a few (1%-6%)
patients for 6 to 12 months. The evidence is sufficient to determine that the technology results
in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
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<tr>
<td>NCT00560651</td>
<td>German Corneal Cross-Linking Registry</td>
<td>7500</td>
<td>Nov 2017 (ongoing)</td>
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<tr>
<td>NCT02721628</td>
<td>Femtosecond Laser Assisted Epi-keratoplasty Versus Collagen Cross-Linking in Progressive Keratoconus</td>
<td>60</td>
<td>Mar 2018</td>
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<tr>
<td>NCT01708538a</td>
<td>Phase III Study of Corneal Collagen Cross-linking Using Two Different Techniques</td>
<td>30</td>
<td>Oct 2018</td>
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<tr>
<td>NCT01189864a</td>
<td>Collagen Crosslinking With Ultraviolet-A in Asymmetric Corneas</td>
<td>500</td>
<td>Dec 2018</td>
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<tr>
<td>NCT01604135</td>
<td>Collagen Crosslinking for Keratoconus - a Randomized Controlled Clinical Trial</td>
<td>200</td>
<td>May 2019</td>
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<tr>
<td>NCT No.</td>
<td>Trial Name</td>
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<td>Completion Date</td>
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<td>----------------------------------------------------------------------------</td>
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<tr>
<td>NCT03319082*</td>
<td>A Phase IV Observational Registry to Assess the Durability of Effect of Corneal Collagen Cross-linking With Photrexa Viscous, Photrexa, and the KXL System in Patients With Corneal Ectasia Following Refractive Surgery</td>
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<td>Jul 2023</td>
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<tr>
<td>Unpublished</td>
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<tr>
<td>NCT01459679</td>
<td>A Multi-Center, Randomized, Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus or Corneal Ectasia After Refractive Surgery</td>
<td>4000</td>
<td>Jan 2016 (terminated)</td>
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<tr>
<td>NCT01344187*</td>
<td>A Multi-Center, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus</td>
<td>236</td>
<td>Jun 2016 (completed)</td>
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<tr>
<td>NCT01972854*</td>
<td>A Multi-Center, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of the KXL System With VibeX (Riboflavin Ophthalmic Solution) for Corneal Collagen Cross-Linking in Eyes With Keratoconus</td>
<td>92</td>
<td>Apr 2017 (terminated)</td>
</tr>
</tbody>
</table>

*NCT: national clinical trial.
*a Denotes industry-sponsored or cosponsored trial.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty society and 1 academic medical center (2 reviewers) while this policy was under review in 2012. The input was mixed, noting the limited literature and lack of U.S. Food and Drug Administration approval for this procedure, although there are ongoing clinical trials regulated by the Food and Drug Administration. Reviewers also commented on the lack of alternatives to slow disease progression, and that data indicated the procedure is safe and effective enough to offer to patients with adequate informed consent under an investigational protocol.
Practice Guidelines and Position Statements

**National Institute for Health and Care Excellence**

In 2013, the National Institute for Health and Care Excellence issued guidance on corneal collagen cross-linking (CXL) using riboflavin and ultraviolet A, updating its 2009 guidance. The 2013 guidance stratified recommendations for corneal CXL as follows:

“Most of the published evidence on photochemical corneal collagen cross-linkage (CXL) using riboflavin and ultraviolet A (UVA) for keratoconus and keratectasia relates to the technique known as ‘epithelium-off CXL’. ‘Epithelium-on (transepithelial) CXL’ 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. Therefore, different recommendations apply to the variants of this procedure, as follows.

1.1 Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia is adequate in quality and quantity. Therefore, this procedure can be used provided that normal arrangements are in place for clinical governance, consent and audit.

1.2 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. Therefore, these procedures should only be used with special arrangements for clinical governance, consent and audit or research.”

**Medicare National Coverage**

There is no national coverage determination.

**Regulatory Status**

In 2016, riboflavin 5’-phosphate in 20% dextran ophthalmic solution (Photrexa Viscous®; Avedro) and riboflavin 5’-phosphate ophthalmic solution (Photrexa®; Avedro) were approved by the Food and Drug Administration for use with KXL System in corneal CXL for the treatment of progressive keratoconus and corneal ectasia after refractive surgery.³
References


7. Avedro Inc. Avedro Briefing Package for Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Device Panel of the Medical Devices Advisory Committee NDA 203324: Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and KXL System (UVA light source) Avedro, Inc. 2015.


9. U.S. Food and Drug Administration. FDA Briefing Package for Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Device Panel of the Medical Devices Advisory Committee NDA 203324: Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and KXL System (UVA light source) Avedro, Inc. 2015.


**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/01/18</td>
<td>New policy, approved October 19, 2018, effective February 1, 2019. Added to Vision Section. This policy was previously archived but it is now being reinstated. Corneal collagen cross-linking using riboflavin and UVA is considered medically necessary as a treatment of progressive keratoconous or corneal ectasia after refractive surgery in those who have failed conservative treatment. It is investigational for all other indications. Added CPT 0402T and HCPC J3490.</td>
</tr>
<tr>
<td>01/11/19</td>
<td>Coding update, added J2787 (new code effective 1/1/19).</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.
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  • Qualified interpreters
  • Information written in other languages
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Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

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https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at:

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