

EFFECTIVE DATE: 08|01|2022

POLICY LAST REVIEWED: 04|15|2026

OVERVIEW

Corneal collagen cross-linking (CXL) is a photochemical procedure approved by the U.S. Food and Drug Administration (FDA) for the treatment of progressive keratoconus and corneal ectasia.

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

Treatment of progressive keratoconus or corneal ectasia after refractive surgery in individuals who have failed conservative treatment (e.g., spectacle correction, rigid contact lens) is covered with one or more of the indications listed below:

Progressive keratoconus or corneal ectasia is defined as 1 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

PRIOR AUTHORIZATION

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products via the online tool for participating providers. Please see Related Policies section below.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

Corneal collagen cross-linking using riboflavin and ultraviolet A may be considered medically necessary as a treatment of progressive keratoconus or corneal ectasia after refractive surgery in individuals who have failed conservative treatment (e.g., spectacle correction, rigid contact lens) when the criteria above are met.

Corneal collagen cross-linking using riboflavin and ultraviolet A is not covered for Medicare Advantage Plans and considered not medically necessary for Commercial Products for all other indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable surgery and not covered benefits/coverage.

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 of over 900 patients keratoconus showed that there was a decrease of 2 high- and 4 low-contrast letters in best-corrected visual acuity over 7-year follow up. 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.

Ectasia (also known as keratectasia, iatrogenic keratoconus, or secondary keratoconus) is a serious long-term complication of laser in situ keratomileusis (LASIK) surgery and photorefractive keratectomy (PRK). 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 of Keratoconus and Ectasia

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 LASIK, although generally, results of these techniques have been poor. Implantation of intrastromal corneal ring segments (see evidence review 9.03.14) 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 (i.e., 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, a penetrating keratoplasty is required.

None of the currently available treatment options for keratoconus and corneal ectasia halt the progression of 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 disease. It is performed with the photosensitizer riboflavin (vitamin B2) and ultraviolet A (UVA) 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 UVA causes the formation of reactive oxygen species, leading to additional covalent bonds (crosslinking) 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-micron 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 FDA is the epithelium-off method. There are no FDA-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.

Two corneal collagen cross-linking products were available for treatment of progressive keratoconus and corneal ectasia – Photrexa and EpiOxa. Photrexa products are planned to be discontinued from the market effective January 20, 2026 with manufacturing set to end February 2026.

For individuals who have progressive keratoconus who receive corneal collagen cross-linking using riboflavin and ultraviolet A, the evidence includes randomized controlled trials (RCTs), systematic reviews, and

nonrandomized studies. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. Based on RCT evidence used to inform FDA approval, corneal collagen cross-linking was associated with significant improvements in corneal curvature score and corrected distance visual acuity and non-significant improvement in uncorrected distance visual acuity compared with sham treatment after 1 year of follow-up. Long-term RCT follow-up is needed. Several non-randomized studies measured visual acuity and found significant and lasting improvements in corrected visual acuity and other measures with corneal collagen cross-linking. The adverse events associated with corneal collagen cross-linking 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% to 6%) patients for 6 to 12 months. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have corneal ectasia after refractive surgery who receive corneal collagen cross-linking using riboflavin and ultraviolet A, the evidence includes systematic reviews and RCTs. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. Systematic reviews demonstrate that corneal collagen cross-linking is effective in reducing the progression of keratoconus and post-laser refractive surgery ectasia. RCT evidence, used to inform FDA approval, found corneal collagen cross-linking associated significant improvements in corneal curvature score, corrected distance visual acuity and uncorrected distance visual acuity after 1 year follow-up when compared with sham treatment. Another trial that followed patients up to 3 years and saw continued improvement in visual acuity with corneal collagen cross-linking. Five-year follow-up in a prospective single-arm study found sustained improvement in uncorrected and corrected distance visual acuity scores and steep keratometry from baseline levels with no significant change in spherical equivalent. Additional long-term follow-up for visual acuity outcomes is needed. The adverse events associated with corneal collagen cross-linking were the same for the ectasia trials as for the keratoconus. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code(s) is considered medically necessary for Medicare Advantage Plans and Commercial Products when the criteria above has been met:

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

RELATED POLICIES

Prior Authorization of Services, Treatments or Procedures

PUBLISHED

Provider Update, June 2026

Provider Update, July 2025

Provider Update, June 2024

Provider Update, May 2023

Provider Update, June 2022

REFERENCES

1. American Academy of Ophthalmology. Corneal Collagen Cross-Linking. October 10, 2024. <https://www.aao.org/eye-health/treatments/corneal-cross-linking-2>. Accessed December 26, 2025.
2. 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; <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=2033> Accessed December 26, 2025.
3. Davis LJ, Schechtman KB, Wilson BS, et al. Longitudinal changes in visual acuity in keratoconus. Invest Ophthalmol Vis Sci. Feb 2006; 47(2): 489-500. PMID 16431941

4. McMahon TT, Edrington TB, Szczotka-Flynn L, et al. Longitudinal changes in corneal curvature in keratoconus. *Cornea*. Apr 2006; 25(3): 296-305. PMID 16633030
5. Epioxa HD and Epioxa. Package insert. Glaukos Corporation; October 2025. <https://www.epioxa.com/wp-content/uploads/2025/10/epioxa-prescribing-information-final.pdf>. Accessed January 7, 2026.
6. Cortina MS, Greiner MA, Kuo AN, et al. Safety and Efficacy of Epithelium-Off Corneal Collagen Cross-Linking for the Treatment of Corneal Ectasia: A Report by the American Academy of Ophthalmology. *Ophthalmology*. Oct 2024; 131(10): 1234-1242. PMID 38935041
7. Hersh PS, Stulting RD, Muller D, et al. United States Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment. *Ophthalmology*. Sep 2017; 124(9): 1259-1270. PMID 28495149
8. McAnena L, Doyle F, O'Keefe M. Cross-linking in children with keratoconus: a systematic review and meta-analysis. *Acta Ophthalmol*. May 2017; 95(3): 229-239. PMID 27678078
9. Toprak I, Yaylali V, Yildirim C. Visual, Topographic, and Pachymetric Effects of Pediatric Corneal Collagen Cross-linking. *J Pediatr Ophthalmol Strabismus*. Mar 01 2017; 54(2): 84-89. PMID 27668869
10. Badawi AE. Accelerated corneal collagen cross-linking in pediatric keratoconus: One year study. *Saudi J Ophthalmol*. 2017; 31(1): 11-18. PMID 28337057
11. Knutsson KA, Paganoni G, Matuska S, et al. Corneal collagen cross-linking in paediatric patients affected by keratoconus. *Br J Ophthalmol*. Feb 2018; 102(2): 248-252. PMID 28655729
12. Papaioannou L, Miligkos M, Papathanassiou M. Corneal Collagen Cross-Linking for Infectious Keratitis: A Systematic Review and Meta-Analysis. *Cornea*. Jan 2016; 35(1): 62-71. PMID 26509768
13. Padmanabhan P, Rachapalle Reddi S, Rajagopal R, et al. Corneal Collagen Cross-Linking for Keratoconus in Pediatric Patients-Long-Term Results. *Cornea*. Feb 2017; 36(2): 138-143. PMID 28060058
14. Raiskup-Wolf F, Hoyer A, Spoerl E, et al. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg*. May 2008; 34(5): 796-801. PMID 18471635
15. Raiskup F, Theuring A, Pillunat LE, et al. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. *J Cataract Refract Surg*. Jan 2015; 41(1): 41-6. PMID 25532633
16. Caporossi A, Mazzotta C, Baiocchi S, et al. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. *Am J Ophthalmol*. Apr 2010; 149(4): 585-93. PMID 20138607
17. Amaral DC, Menezes AHG, Vilaça Lima LC, et al. Corneal Collagen Crosslinking for Ectasia After Refractive Surgery: A Systematic Review and Meta-Analysis. *Clin Ophthalmol*. 2024; 18: 865-879. PMID 38525385
18. Hersh PS, Stulting RD, Muller D, et al. U.S. Multicenter Clinical Trial of Corneal Collagen Crosslinking for Treatment of Corneal Ectasia after Refractive Surgery. *Ophthalmology*. Oct 2017; 124(10): 1475-1484. PMID 28655538
19. Wittig-Silva C, Whiting M, Lamoureux E, et al. A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. *J Refract Surg*. Sep 2008; 24(7): S720-5. PMID 18811118
20. Wittig-Silva C, Chan E, Islam FM, et al. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology*. Apr 2014; 121(4): 812-21. PMID 24393351
21. Margines JB, Rabinowitz YS, Li X, et al. Results of corneal collagen cross-linking in patients with corneal ectasia after laser refractive surgery-A prospective study. *Photodiagnosis Photodyn Ther*. Jun 2023; 42: 103521. PMID 36931367
22. Center for Drug Evaluation and Research. Application Number 203324Orig2s000. Summary Review. 2015; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/203324Orig2s000SumR.pdf. Accessed December 26, 2025.
23. National Institute for Health and Care Excellence (NICE). Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus and keratectasia [IPG466]. 2013; <https://www.nice.org.uk/guidance/ipg466>. Accessed December 26, 2025.

CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS

This medical policy is made available to you for informational purposes only. It is not a guarantee of payment or a substitute for your medical judgment in the treatment of your patients. Benefits and eligibility are determined by the member's subscriber agreement or member certificate and/or the employer agreement, and those documents will supersede the provisions of this medical policy. For information on member-specific benefits, call the provider call center. If you provide services to a member which are determined to not be medically necessary (or in some cases medically necessary services which are non-covered benefits), you may not charge the member for the services unless you have informed the member and they have agreed in writing in advance to continue with the treatment at their own expense. Please refer to your participation agreement(s) for the applicable provisions. This policy is current at the time of publication; however, medical practices, technology, and knowledge are constantly changing. BCBSRI reserves the right to review and revise this policy for any reason and at any time, with or without notice. Blue Cross & Blue Shield of Rhode Island is an independent licensee of the Blue Cross and Blue Shield Association.

