MEDICAL POLICY

POLICY TITLE	CORNEAL COLLAGEN CROSS-LINKING
POLICY NUMBER	MP 2.028

CLINICAL BENEFIT	☒ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective date:	**7/1/2026**

POLICY

Corneal Collagen Cross-Linking

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).

Corneal collagen cross-linking using riboflavin and ultraviolet A is considered **investigational** for all other indications as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures.

POLICY GUIDELINES

The American Academy of Ophthalmology has not set forth definitive criteria defining progressive keratoconus, but has suggested that signs of progression include changes in refraction, visual acuity and corneal shape. In the trials leading to U.S Food and Drug Administration (FDA) approval of corneal collagen cross-linking, progressive keratoconus or corneal ectasia were 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.

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.

Cross-References:
MP 1.044 Implantation of Intrastromal Corneal Ring Segments
MP 1.159 Amniotic Membrane for Ocular Indications
MP 9.011 Corneal Surgery

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PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO - Refer to FEP medical policy manual. The FEP medical policy manual can be found at: fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

DESCRIPTION/BACKGROUND

Corneal collagen cross-linking is a photochemical procedure approved by the FDA for the treatment of progressive keratoconus and corneal ectasia following refractive surgery. Keratoconus is a dystrophy of the cornea characterized by progressive deformation (steepening) of the cornea, while corneal ectasia is keratoconus that occurs following refractive surgery. Both conditions can lead to functional loss of vision and need for corneal transplantation.

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 laser in situ keratomileuses, 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 (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, 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 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 corneal collagen cross-linking:

1. Epithelium-off corneal collagen cross-linking (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-mm thick stroma (endothelium, anterior chamber, iris, lens, retina) are not exposed to an ultraviolet dose that is above the cytotoxic threshold.

2. Epithelium-on corneal collagen cross-linking (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.

Historically, the only corneal collagen cross-linking treatment approved by the FDA was the epithelium-off method. In 2025, the first epithelium-on corneal collagen cross-linking treatment was approved (riboflavin 5'-phosphate ophthalmic solution, 0.177% and 0.239%; Epioxa™). Epoxia is anticipated to enter the market during quarter 1 of 2026. Corneal collagen cross-linking is being evaluated primarily for corneal stabilization in patients with progressive corneal thinning, such as keratoconus and corneal ectasia following refractive surgery. Corneal collagen cross-linking may also have anti-edematous and antimicrobial properties.

Regulatory Status

In 2016, riboflavin 5'-phosphate in 20% dextran ophthalmic solution (Photrexa Viscous™; Avedro now Glaukos) and riboflavin 5'-phosphate ophthalmic solution (Photrexa™; Avedro) were approved by the FDA for use with the KXL System in corneal corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia after refractive surgery. In 2025, riboflavin 5'-phosphate 0.177% and 0.239% ophthalmic solution (Epioxa™ and Epioxa HD™; Glaukos) was approved for treatment of keratoconus in adults and children aged 13 years and older. Epioxa uses the O2n System™ and Boost Googles® for its proprietary epithelium-on corneal collagen cross-linking technology.Photrexa products are planned to be discontinued from the market effective January 20, 2026 with manufacturing set to end February 2026.

RATIONALE

SUMMARY OF EVIDENCE

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. For epithelium-on corneal collagen cross-linking, 2 RCTs showed a significant difference between corneal cross-linking and sham treatment in maximum corneal curvature, but visual acuity results are lacking. Based on RCT evidence used to inform FDA approval, epithelium-off 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 epithelium-off 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.

DEFINITIONS

CORNEA refers to the transparent anterior portion of the sclera (the fibrous outer layer of the eyeball), about one sixth of its surface: the first part of the eye that refracts light.

ENDOTHELIUM refers to the layer of simple squamous epithelial cells that line the heart, the blood and the lymph vessels, and the serous cavities of the body.

INTRAOCULAR LENS is a mechanical transplant used in ophthalmology to replace the natural lens of the eye that has ceased to function due to disease (e.g., cataract) or otherwise functionally disrupted.

ORTHOPTICS is the science of correcting defects in binocular vision resulting from defects in optic musculature.

PSEUDOPHAKIA is a condition in which the natural lens of the eye is replaced with an intraocular lens.

REFRACTION is a routine test used by eye specialists to measure refractive errors of the eye.

REFRACTIVE ERRORS are eye conditions correctable with eyeglasses (e.g., myopia, astigmatism).

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DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary, corneal collagen cross linking:

Procedure Codes							
0402T	J2787	J2789					

ICD-10-CM Diagnosis Codes	Description
H18.601	Keratoconus, unspecified, right eye
H18.602	Keratoconus, unspecified, left eye
H18.603	Keratoconus, unspecified, bilateral
H18.609	Keratoconus, unspecified, unspecified eye
H18.611	Keratoconus, stable, right eye
H18.612	Keratoconus, stable, left eye
H18.613	Keratoconus, stable, bilateral
H18.619	Keratoconus, stable, unspecified eye
H18.621	Keratoconus, unstable, right eye
H18.622	Keratoconus, unstable, left eye
H18.623	Keratoconus, unstable, bilateral
H18.629	Keratoconus, unstable, unspecified eye

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ICD-10-CM Diagnosis Codes	Description
H18.711	Corneal ectasia, right eye
H18.712	Corneal ectasia, left eye
H18.713	Corneal ectasia, bilateral
H18.719	Corneal ectasia, unspecified eye

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POLICY HISTORY

MP 2.028	**06/15/2020 Consensus Review.** No change to Policy Statement. Product Variation updated. Coding reviewed, no changes. References reviewed and updated.
	07/14/2021 Consensus Review. Updated FEP, Background, Rationale, and References. No changes to coding. Updated coding tables for ICD-10 and HCPCS.

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	06/06/2022 Consensus Review. No change to policy statement. Product Variations updated. Coding table format updated. References reviewed and updated.
	04/14/2023 Consensus Review. No change to policy statement. References reviewed and updated. Coding reviewed.
	05/09/2024 Consensus Review. No change to policy statement. References reviewed and updated. Coding reviewed with no changes.
	06/18/2025 Major Review. Title changed to Corneal Collagen Cross-Linking. Removed Corneal Pachymetry, Corneal Endothelial Microscopy and Transciliary Fistulization criteria. Background, Rationale, Definitions and References updated. Removed codes 66999, 76514, 92286, H17.11, H17.12, H17.13, H18.011, H18.012, H18.013, H18.051, H18.052, H18.053, H18.061, H18.062, H18.063, H18.51. H18.52, H18.53, H18.54, H18.55, H18.59, H18.711, H18.712, H18.713, H18.719, H18.891, H18.892, H18.893, H40.011, H40.012, H40.013, H40.021, H40.022, H40.023, H40.031, H40.032, H40.033, H40.041, H40.042, H40.043, H40.051, H40.052, H40.053, H40.061, H40.062, H40.063, H40.1111, H40.1112, H40.1113, H40.1114, H40.1121, H40.1122, H40.1123, H40.1124, H40.1131, H40.1132, H40.1133, H40.1134, H40.1211, H40.1212, H40.1213, H40.1214, H40.1221, H40.1222, H40.1223, H40.1224, H40.1231, H40.1232, H40.1233, H40.1234, H40.1311, H40.1312, H40.1313, H40.1314, H40.1321, H40.1322, H40.1323, H40.1324, H40.1331, H40.1332, H40.1333, H40.1334, H40.1411, H40.1412, H40.1413, H40.1414, H40.1421, H40.1422, H40.1423, H40.1424, H40.1431, H40.1432, H40.1433, H40.1434, H40.151, H40.152, H40.153, H40.211, H40.212, H40.2211, H40.2212, H40.2213, H40.2214, H40.2221, H40.2222, H40.2223, H40.2224, H40.2231, H40.2232, H40.2233, H40.2234, H40.231, H40.232, H40.233, H40.241, H40.242, H40.243, H40.31X1, H40.31X2, H40.31X3, H40.31X4, H40.32X1, H40.32X2, H40.32X3, H40.32X4, H40.33X1, H40.33X2, H40.33X3, H40.33X4, H40.41X1, H40.41X2, H40.41X3, H40.41X4, H40.42X1, H40.42X2, H40.42X3, H40.42X4, H40.43X1, H40.43X2, H40.43X3, H40.43X4, H40.51X1, H40.51X2, H40.51X3, H40.51X4, H40.52X1, H40.52X2, H40.52X3, H40.52X4, H40.53X1, H40.53X2, H40.53X3, H40.53X4, H40.61X1, H40.61X2, H40.61X3, H40.61X4, H40.62X1, H40.62X2, H40.62X3, H40.62X4, H40.63X1, H40.63X2, H40.63X3, H40.63X4, H40.811, H40.812, H40.813, H40.821, H40.822, H40.823, H40.831, H40.832, H40.833, H40.89, H42, H44.511, H44.512, H44.513, L12.0, L12.1, L12.2, L12.31, L12.35, L12.8, T86.840, T86.841, Z01.818, Z46.0, Z94.7, Z96.1.
	10/09/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/05/2026 Consensus Review. No change to policy statement. Policy Guidelines, Background, and Rationale updated. References added.
	06/03/2026 Administrative Update. Added New Code J2789. Eff date 07/01/2026

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