BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Corneal Collagen Cross-Linking

Policy #: 639
Latest Review Date: April 2025
Category: Vision

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **corneal collagen cross-linking using riboflavin and ultraviolet A** as a **covered benefit** for treatment of progressive keratoconus or corneal ectasia not arising from keratorefractive surgery in individuals who have failed conservative treatment (e.g., spectacle correction, rigid contact lens).

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

- An increase of 1 diopter (D) in the steepest keratometry value
- An increase of 1 diopter (D) in regular astigmatism evaluated by subjective manifest refraction
- A myopic shift (decrease in the spherical equivalent) of 0.50 diopter (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.

Blue Advantage will treat **corneal collagen cross-linking using riboflavin and ultraviolet A** as a **non-covered benefit** and as **investigational** for all other indications.

Treatment of complications or surgical procedures, including corneal collagen cross-linking, arising from post-keratorefractive surgery (e.g. LASIK) corneal ectasia are not covered, even if medically necessary. Refractive surgery is a benefit exclusion.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Corneal collagen cross-linking is a photochemical procedure approved by the Food and Drug Administration (FDA) 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.

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

keratomileusis (LASIK), 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 individuals 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 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 disease. It is performed with the photosensitizer riboflavin (vitamin B_2) and ultraviolet A irradiation. There are two protocols for corneal collagen cross-linking:

1. Epithelium-off corneal collagen cross-linking (also known as "epi-off"): In this method, about eight 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 one to three 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 (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 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 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.

Currently, the only corneal collagen cross-linking treatment approved by the Food and Drug Administration (FDA) is the epithelium-off method. There are no FDA-approved corneal collagen cross-linking treatments using the epithelium-on method. Corneal collagen cross-linking is being evaluated primarily for corneal stabilization in individuals 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.

KEY POINTS:

The most recent literature update was performed through January 15, 2025.

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. 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 follow-up. Long-term RCT follow-up is needed. Several non-randomized studies measured 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%-6%) individuals for 6 to 12 months. The evidence is sufficient to determine that technology results in an improvement in net health outcomes.

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 with 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. A 5-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 the 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 technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements
National Institute for Health and Care Excellence
In 2013, the National Institute for Health and Care Excellence (NICE) issued guidance on corneal collagen cross-linking using riboflavin and ultraviolet A, updating its guidance based on a 2009 systematic review of primarily low-quality evidence; review authors declared no financial conflicts of interest. The 2013 guidance stratified recommendations for corneal collagen cross-linking as follows:

"Most of the published evidence on photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A (UVA) for keratoconus and keratectasia relates to the technique known as 'epithelium-off corneal collagen cross-linking'. 'Epithelium-on (transepithelial) corneal collagen cross-linking' is a more recent technique and less evidence is available on its safety and efficacy. Either procedure (epithelium-off or epithelium-on corneal collagen cross-linking) can be combined with other interventions, and the evidence base for these combination

procedures (known as 'corneal collagen cross-linking plus') is also limited. Therefore, different recommendations apply to the variants of this procedure, as follows.

- Current evidence on the safety and efficacy of epithelium-off corneal collagen cross-linking 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.
- Current evidence on the safety and efficacy of epithelium-on (transepithelial) corneal collagen cross-linking, and the combination (corneal collagen cross-linking 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."

U.S. Preventive Services Task Force Recommendations
Not applicable.

KEY WORDS:
Corneal Collagen Cross-linking, refractory surgery, LASIK, Keratoconus, Photrexa Viscous®; Avedro, Photrexa®; Avedro, corneal ectasia, CXL, KXL

APPROVED BY GOVERNING BODIES:
Epithelium-off corneal cross-linking performed with Photrexa® Drug Formulations, Photrexa® Viscous, Photrexa® and KXL® System is the only cross-linking procedure approved by the FDA.

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT Codes:

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

HCPCS Codes:

J2787	Riboflavin 5'-phosphate, ophthalmic solution, up to 3 ml

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POLICY HISTORY:

Adopted for Blue Advantage, April 2017
Available for comment April 28 through June 11, 2017
Medical Policy Group, March 2018
Medical Policy Group, June 2018
Medical Policy Group, December 2018: 2019 Annual Coding Update
Medical Policy Group, April 2019
Medical Policy Group, March 2020
Medical Policy Group, March 2021
Medical Policy Group, March 2022
Medical Policy Group, June 2022: Quarterly coding update. CPT code 0402T revised to include "epi on" as well as "epi off" by adding the verbiage "when performed" to code description.
Medical Policy Group, March 2023
Medical Policy Group, November 2023: Clarification to policy statement regarding the coverage of corneal ectasia not arising from keratorefractive surgery. No change to policy intent. Updated note stating complications/procedures associated with keratorefractive surgery are not covered. Refractive surgery is a benefit exclusion.
UM Committee, December 2023: Policy approved by UM Committee for use for Blue Advantage business.
Medical Policy Group, April 2024
UM Committee, April 2024: Annual review of policy approved by UM Committee for use for Blue Advantage business.
Medical Policy Group, April 2025
UM Committee, April 2025: Annual review of policy approved by UM Committee for use for Blue Advantage business.
