

Corporate Medical Policy

Corneal Collagen Cross-linking

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Description of Procedure or Service

Corneal collagen cross-linking (CXL) is a photochemical procedure 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 vision loss and need for corneal transplantation.

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 (BCVA). 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 (LASIK) 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 (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 (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, 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

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 (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 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 (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.

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 U.S. Food and Drug Administration for use with KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia after refractive surgery.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for corneal collagen cross-linking when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member’s Benefit Booklet for availability of benefits. Member’s benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Corneal Collagen Cross-linking is covered

Corneal collagen cross-linking using riboflavin and ultraviolet A may be considered medically necessary as a treatment of:

- a) progressive keratoconus **OR**
- b) corneal ectasia after refractive surgery in patients who have failed conservative treatment (eg spectacle correction, rigid contact lens).

Corneal Collagen Cross-linking

When Corneal Collagen Cross-linking is not covered

Corneal collagen cross-linking using riboflavin and ultraviolet A is considered investigational for all other indications.

Policy Guidelines

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.

For individuals who have progressive keratoconus who receive CXL using riboflavin and ultraviolet A, the evidence includes multiple randomized controlled trials (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 diopter (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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0402T, J2186, J2787

Corneal Collagen Cross-linking

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

National Institute for Health and Clinical Excellence (NICE). Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus. 2009. Available online at: <http://www.nice.org.uk/nicemedia/live/12119/46253/46253.pdf> . Last accessed September 2011.

National Keratoconus Foundation. Corneal Crosslinking Sites in the US. Available online at: <http://www.nkcf.org/en/treatment-options/corneal-crosslinking/159-us-cxl-sites-2.html> . Last accessed February 2012.

BCBSA Medical Policy Reference Manual [Electronic Version]. 9.03.28, 3/8/2012

Specialty Matched Consultant Advisory Panel- 6/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 9.03.28, 3/14/13

Specialty Matched Consultant Advisory Panel 6/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 9.03.28, 4/10/14

Specialty Matched Consultant Advisory Panel- 6/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 9.03.28, 4/23/15

Specialty Matched Consultant Advisory Panel- 6/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 9.03.28, 3/10/16

Specialty Matched Consultant Advisory Panel- 6/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 9.03.28, 3/9/17

Medical Director review 3/2017

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Specialty Matched Consultant Advisory Panel- 6/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 9.03.28, 3/8/2018

Medical Director review 10/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 9.03.28, 3/14/2019

Specialty Matched Consultant Advisory Panel- 6/2019

Medical Director review 6/2019

Policy Implementation/Update Information

Corneal Collagen Cross-linking

- 7/10/12 New policy issued. Corneal collagen cross-linking is considered **investigational**. BCBSNC does not provide coverage for investigational services or procedures. Medical director review 6/2012. Specialty Matched consultant advisory panel review meeting 6/20/12. Notification given 7/10/12. Effective date 10/16/2012. (lpr)
- 4/16/13 Reference added. No change to policy statement. (lpr)
- 7/16/13 Specialty matched consultant advisory panel review 6/19/2013. No change to policy statement. (lpr)
- 5/27/14 Reference updated. Updated regulatory status. No change to policy statement. (lpr)
- 7/15/14 Specialty matched consultant advisory panel review meeting 6/24/2014. No change to policy statement. (lpr)
- 7/28/15 Updated Regulatory Status and Policy Guidelines sections. Reference added. Specialty Matched Consultant Advisory Panel review 6/24/2015. No change to policy statement. (lpr)
- 12/30/15 Added CPT code 0402T to Billing/Coding section for effective date 1/1/2016. (lpr)
- 4/29/16 Updated Policy Guidelines and Regulatory Status. Reference added. No change to policy statement. (lpr)
- 7/26/16 Specialty Matched Consultant Advisory Panel review 6/29/2016. No change to policy statement. (lpr)
- 4/28/17 Updated Description section. Reference added. Medical Director review 3/2017. No change to policy statement. (lpr)
- 7/28/17 Specialty Matched Consultant Panel review 6/28/2017. No change to policy statement. (lpr)
- 8/10/18 Specialty Matched Consultant Panel review 6/2018. No change to policy statement. Reference added. (lpr)
- 10/26/18 Under “When Covered” section, added medical necessity coverage criteria: “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 patients who have failed conservative treatment (eg spectacle correction, rigid contact lens).” Updated Policy Guidelines section. Medical Director review 10/2018. (lpr)
- 12/31/18 Added HCPC codes J2186 and J2787 to the Billing/Coding section effective 1/1/19. (lpr)
- 4/1/19 Policy archived. (lpr)
- 4/30/19 Policy archived in error- back to active status. (lpr)
- 7/1/19 Specialty Matched Consultant Advisory Panel review 6/17/2019. Reference added. Realigned language in “When Covered” section for clarity. No change to policy intent. (lpr)

Corneal Collagen Cross-linking

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.