Corneal Collagen Cross-linking

Description of Procedure or Service

Corneal collagen cross-linking (CXL) is a photochemical procedure that is being evaluated as a method to stabilize the cornea in patients with progressive keratoclasia such as keratoconus and pellucid marginal degeneration. CXL may also have anti-edematous and antimicrobial properties and has been evaluated for the treatment of bullous keratopathy and infectious keratitis.

**Background**

Corneal collagen cross-linking (CXL) is performed with the photosensitizer riboflavin (vitamin B₂) and ultraviolet-A (UVA) irradiation. A common CXL protocol removes about 8 mm of the central corneal epithelium 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 370 nm UVA, a maximal wavelength for absorption by riboflavin, together with the continued application of riboflavin. The interaction of riboflavin and UVA causes the formation of reactive oxygen species, leading to additional covalent bonds (cross-linking) between collagen molecules that results 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, and retina) are not exposed to a UV dose that is above the cytotoxic threshold.

CXL is being evaluated primarily for corneal stabilization in patients with progressive corneal thinning such as keratoconus. CXL may also have anti-edematous and antimicrobial properties.

Keratoconus is a bilateral dystrophy that is characterized by progressive ectasia (paracentral steepening and stromal thinning) that impairs visual acuity. The progression of keratoconus is highly variable. Initial treatment 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, but in general, results of these techniques have been poor. Implantation of intrastromal corneal ring segments (see policy 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 a penetrating keratoplasty. A 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. In contrast, CXL has the potential to slow the progression of disease.

Pellucid marginal degeneration is a noninflammatory progressive degenerative disease, typically characterized by bilateral peripheral thinning (ectasia) of the inferior cornea. Deterioration of visual function results from the irregular astigmatism induced by asymmetric distortion of the cornea, and visual acuity typically cannot be restored by using sphero-cylindrical lenses. Rigid gas permeable contact lenses may be used to treat pellucid marginal degeneration. Intrastromal ring segment implantation, crescentic lamellar keratoplasty, penetrating keratoplasty, and corneal wedge excision
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have also been proposed.

**Regulatory Status**

No UVA devices have received clearance or premarket approval for the treatment of keratoconus in the U.S. A search of online site Clinicaltrials.gov shows ongoing Phase III safety and efficacy trials of UV-A Illumination Systems by Topcon Medical (VEGA) and Avedro Inc. (KXL or UV-X). The FDA has granted Avedro Inc, a priority review of their new drug application (NDA) for the riboflavin ophthalmic solution/KXL II system as an orphan drug (fewer than 200,000 individuals affected in the U.S). If approved, Avedro would have 7 years of market exclusively in the U.S. In October 2015 Avedro resubmitted their NDA to the FDA. The KXL II system is currently approved for use in Europe.

***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**

Corneal collagen cross-linking is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

**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**

Not Applicable

**When Corneal Collagen Cross-linking is not covered**

Corneal collagen cross-linking is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

**Policy Guidelines**

The evidence for corneal CXL in individuals who have keratoconus includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. There is evidence from RCTs, including several pivotal trials, that CXL leads to short-term improvements in corneal steepening and visual acuity compared with untreated eyes, and results from 1 trial have reported that these benefits are maintained at 2 to 3 years. From these RCTs, one can conclude that CXL reduces, and in some cases, reverses the corneal steepening that leads to a reduction in visual acuity in the short term. Greater uncertainty exists regarding the long-term outcomes of corneal CXL for the treatment of keratoconus. Some retrospective studies have reported positive outcomes to 10 years, although these reports have small sample sizes at long-term follow-up and limited information on the entire population of patients treated with corneal CXL during the same time period. There is a need for prospective studies with larger numbers of patients who are followed over many years to determine whether corneal CXL improves longer term outcomes. Several trials are ongoing, and their results are expected soon. Longer term outcomes from large cohorts will also be useful to evaluate potential long-term complications of this new treatment approach. Although one device is currently under U.S. Food and Drug Administration...
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(FDA) review, no corneal CXL devices have received FDA approval at this time. The evidence is insufficient to determine the effects of the technology on health outcomes.

**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*

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**


**Policy Implementation/Update Information**

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)
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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)


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)

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.