Clinical Policy: Corneal Collagen Cross-linking

Reference Number: HNCA.CP.MP.603 Coding Implications
Last Review Date: 09/19 Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Collagen cross-linking (CXL) is a procedure that uses riboflavin eye drops (Vitamin B_2), ultraviolet light, and a photosensitizer to change the cross links within the collagen fibers in the cornea. The intent is to prevent the progression of keratoconus and cornea ectasia (keratectasia) by strengthening the collagen bonds, thereby increasing corneal rigidity and stability.

Policy/Criteria

I. It is the policy of Health Net of California that epithelium-off collagen cross-linking using riboflavin and ultraviolet A is considered **medically necessary** for the treatment of keratoconus and keratectasia.

II. It is the policy of Health Net of California that epithelium-on (transepithelial) collagen cross-linking is considered **investigational** for keratoconus, keratectasia, and all other indications.

III. It is the policy of Health Net of California that any type of collagen cross-linking is considered **investigational** in all other situations, including but not limited to treatment of infectious keratitis and in combination with other procedures (e.g., intrastromal corneal ring segments, PRK or phakic intra-ocular lens implantation) (CXL-plus).

Background
Corneal ectasia is a non-inflammatory condition, the hallmark of which is progressive corneal steepening and thinning. Types of corneal ectasia include keratoconus, pellucid marginal degeneration, keratoglobus, post kerato refractive ectasia, and wound ectasia after penetrating keratoplasty (PK). Corneal ectasia can be a serious long-term complication of LASIK surgery that is estimated to occur in 0.004% to 0.6% of post LASIK patients. Corneal ectasias are associated with decreased uncorrected visual acuity, an increase in ocular aberrations, and often a loss of best-corrected distance visual acuity. Corneal ectasias can result in significant ocular morbidity and may require surgical intervention.

Keratoconus is the most common corneal degenerative disorder, with prevalence estimates varying from 760 to 3300 cases per 100,000 people. It is characterized by progressive (usually bilateral) ectasia where collagen fibers within the cornea weaken so the normally round shape progressively develops into more of a conical appearance. This causes the cornea to bulge outward and steepen. This abnormal shape prevents light entering the eye from focusing directly on the retina, resulting in irregular astigmatism and progressive myopia or visual loss.

CLINICAL POLICY
CORNEAL CROSS-LINKING

Treatments to improve the refractive errors caused by keratoconus have included hard contact lenses and surgical techniques such as photorefractive keratectomy and implantation of intrastromal rings. Penetrating keratoplasty (i.e., corneal grafting) is considered as the last resort. These treatments, however, are not disease modifying, whereas corneal cross-linking has the potential to slow the progression of disease. In April 2016, the U.S. Food and Drug Administration (FDA) gave approval to Avedro Inc.'s corneal cross-linking system to treat patients with progressive keratoconus and post-LASIK ectasia.

According to the National Institute for Health and Care Excellence (NICE), there are two different methods of cross-linking the collagen in the cornea. In epithelium-off CXL (also known as "epi-off"), the epithelium is first removed or weakened, typically by abrasion, to allow penetration of riboflavin into the corneal tissue. Riboflavin eye drops are applied to the corneal surface before the procedure and intermittently during the procedure. The corneal surface is then exposed to UVA radiation. Postoperatively, topical antibiotics and anti-inflammatory drops are normally prescribed, with topical steroids if necessary. In some cases, a bandage contact lens may also be used for a few days. The procedure is done on 1 eye at a time and may also be repeated if needed. The Epi-off procedure is currently FDA approved.

In epithelium-on (also known as "epi-on" or transepithelial) CXL, the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed. There are no FDA approved CXL treatments using the epithelium-on method of CXL

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2013) concluded that there is adequate evidence on the safety and efficacy of epithelium-off CXL using riboflavin and ultraviolet A for keratoconus and keratectasia. NICE found inadequate evidence of the safety and efficacy of epithelium-on (transepithelial) CXL.

HAYES (2018) reports on 23 studies, including 9 randomized controlled trials (RCTs), 2 prospective trials with historical controls, 6 prospective comparative cohort studies, and 6 retrospective comparative cohort studies of patients with documented keratoconus. Sample sizes ranged for 50 to 200 eyes comparing sham treatments to epi- on and epi-off procedures and follow-up ranged from 1 to 3 years. Outcome measures included corneal topography, including maximum keratometry (Kmax), average keratometry (Km), keratometry in flat meridian (K1), keratometry in steep meridian (K2); visual acuity, including best-spectacle-corrected visual acuity (BSCVA), corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA); refraction measures, including spherical equivalent (SE), spherical error, cylindrical error; corneal thickness measured by central corneal thickness (CCT) or thinnest point corneal thickness (TPCT); adverse events (AEs)

HAYES concluded that evidence from the available studies suggests that C-CXL may slow or stop progression of keratoconus relative to no treatment or sham treatment as indicated by altered corneal topography, specifically, flattening of the cornea. Findings were inconsistent for visual

acuity and corneal thickness outcomes, and C-CXL does not seem to impact measures of refraction. C-CXL appears to be generally safe, with impaired epithelial healing and corneal haze as the most commonly reported complications. The available studies were relatively small, with intermediate-term follow-up (1-3 years); therefore, the long-term efficacy and safety of the procedure are not known.

According to UptoDate, corneal collagen cross-linking is recommended for the management of keratoconus. It has been shown to slow the progression by strengthening collagen fibers. In patients with stable disease, advanced ectatic disease (cornea is too thin), or severe scarring, correction of visual impairment may require spectacles, contact lenses, or surgical interventions. Collagen cross-linking is generally not performed in patients with active or history of herpes simplex virus (HSV) keratitis, thin corneas, or corneal hydrops.

Hersh et al. studied data from 2 multicenter trials of corneal collagen cross-linking (CXL) for keratoconus and noted beneficial effects on disease progression. In the concurrent studies, 205 patients with keratoconus (mean age, 33 years) were assigned randomly to either standard ultraviolet A–riboflavin 0.1% CXL treatment (n = 102 eyes) or sham treatment (riboflavin 0.1% with dextran, no epithelial removal or irradiation; n = 103 eyes). The primary efficacy endpoint was the between-group difference in maximum keratometry change over 1 year. Secondary endpoints were corrected and uncorrected distance visual acuity (CDVA and UDVA, respectively), manifest refraction spherical equivalent (MRSE), endothelial cell count, and adverse events.

Ninety CXL eyes and 76 control eyes were followed for 12 months. The mean decrease in maximum keratometry value in the CXL group was 1.6 ± 4.2 D during the 1-year period; a decrease of ≥ 2.0 D occurred in 28 eyes (31.5%) and an increase of ≥ 2 D occurred in 5 eyes (5.6%). In contrast, the control group had a mean increase of 1.0 ± 5.1 D. The difference in maximum keratometry change between the study groups was 2.6 D. CDVA in the CXL group improved by 5.7 logMAR letters, with 23 of 83 eyes (27.7%) gaining and 5 eyes (6%) losing ≥ 10 letters. UDVA improved by 4.4 logMAR letters in the CXL group. Corneal haze was the most common adverse effect of CXL. The endothelial cell count did not change significantly during the year following treatment, and the between-group differences in MRSE changes were not significant.

The authors concluded that CXL treatment effectively and safely halts the progression of keratoconus, findings supported by several international studies. The benefits include reduced corneal steepness, better visual acuity, and improved subjective function. Transient or permanent corneal haze was the most frequently reported adverse event. Earlier randomized controlled trials and cohort studies of collagen cross-linking demonstrated flattening of the cornea and improvement in visual, topographic, and wavefront parameters that were maintained for up to seven years.

Coding Implications

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CPT®* Codes	Description
0402T	Collagen cross-hyphenlinking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed)

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ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Code	Description
H18.601 - H18.629	Keratoconus
H18.711 - H18.719	Corneal ectasia

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed.	9/18	9/18
Update, no changes	9/19	9/19

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CLINICAL POLICY
CORNEAL CROSS-LINKING

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

CLINICAL POLICY
CORNEAL CROSS-LINKING

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.