Coverage Policy Manual
Policy #: 2014011
Category: Medicine
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Corneal Collagen Cross-linking

Description:

Corneal collagen cross-linking (CXL) is a photochemical procedure that is being evaluated as a method to stabilize the cornea in patients with progressive keratectasia such as keratoconus and pellucid marginal degeneration. CXL may also have anti-edematous and antimicrobial properties and has been evaluated for the treatment of corneal edema, 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 # 2005012) 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.

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.

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 spherocylindrical 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 have also been proposed.

Treatment
The initial treatment for keratoconus often consists of hard contact lenses. A variety of kerato-refractive 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 (see evidence review 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 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 (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 â€œepi-offâ€): 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 â€œepi-onâ€ 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.
Progressive keratoconus or corneal ectasia is defined as 1 or more of the following:

- An increase of 1 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 â‰¥0.1 mm in the back optical zone radius in rigid contact lens wearers where other information was not available.

Regulatory Status
In 2016, riboflavin 5Â¢-phosphate in 20% dextran ophthalmic solution (Photrexa ViscousÂ®; Avedro) and riboflavin 5 Â¢-phosphate ophthalmic solution (PhotrexaÂ®; 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 (PhotrexaÂ®, Avedro).

Coding
There is a specific CPT category III code for this service:
0402T: Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed)

It may be reported using CPT code 66999 - unlisted procedure, anterior segment of eye.

Policy/ Coverage:

Meets Primary Coverage Criteria Or Is Covered For Contracts Without Primary Coverage Criteria

Effective August 2017
Corneal collagen cross-linking using riboflavin and ultraviolet A meets member benefit certificate primary coverage criteria that there be scientific evidence of effectiveness in improving health outcomes 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).

Does Not Meet Primary Coverage Criteria Or Is Investigational For Contracts Without Primary Coverage Criteria

For members with contracts without primary coverage criteria, corneal collagen cross-linking using riboflavin and ultraviolet A, for all other indications, does not meet member benefit certificate primary coverage criteria because there is a lack of scientific evidence of effectiveness.

For members with contracts without primary coverage criteria, the use of corneal collagen crosslinking for all other indications is considered investigational. Investigational services are specific contract exclusions in most member benefit certificates of coverage.

Effective Prior to August 2017

The use of corneal collagen cross-linking for any indication does not meet member benefit certificate primary coverage criteria.

For members with contracts without primary coverage criteria, the use of corneal collagen cross-linking for any indication is considered investigational. Investigational services are specific contract exclusions in most member benefit certificates of coverage.

Rationale:

Natural History of Keratoconus
The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study is a multi-center long-term observational study of the natural history of keratoconus. Two reports were published from the CLEK study in 2006 that showed slow changes over 7 years of follow-up (Davis, 2006; McMahon, 2006). Davis et al reported changes in high- and low-contrast visual acuity from 953 patients (1855 eyes) (Davis, 2006). Over a period of 7 years, there was a decrease of 2 high- and 4 low-contrast letters. High-contrast visual acuity decreases of 10 or more letters occurred in 19.0% of patients; low-contrast visual acuity decreases of 10 or more letters occurred in 30.8% of patients. McMahon et al reported longitudinal changes in corneal curvature over 8 years of follow-up in 1032 patients (McMahon, 2006). The slope for First Definite Apical Clearance Lens (FDACL) was 0.18 diopters (D) per year, and the slope for flatter keratometric reading (Flat K) was 0.20 D per year. These

translated into mean increases of 1.44 D in FDACL and 1.6 D in Flat K during the 8-year follow-up period. Close to 25% of patients had projected increases of 3 D or more in FDACL, while 24% had projected increases of 3 D or more in Flat K.

Evidence Review
Evidence on whether corneal collagen cross-linking (CXL) improves health outcomes for patients with progressive keratoconus consists of 4 controlled trials, 3 of which are randomized. In addition, there are uncontrolled trials that report on longer-term outcomes of the procedure. The main health outcome for CXL treatment is improvement, or stabilization, of visual acuity. Other outcomes commonly reported in trials of CXL include physiologic measures, such as the steepness of the corneal curvature and/or the manifest refraction spherical equivalent (MRSE). These are intermediate outcomes that may corroborate whether improvements in visual acuity correlate with physiologic changes, and which may or may not be adequate surrogates for true health outcomes.

Controlled Trials

Wittig-Silva et al reported the first randomized controlled trial (RCT) of corneal CXL in 2008 (Wittig-Silva, 2008). Three-year results were published in 2014 (Wittig-Silva, 2014). Recruitment for the trial was completed in 2009 with 50 eyes randomized to CXL and 50 randomized to untreated control. To be eligible for enrollment, clear evidence of progression of the ectasia over the preceding 6 to 12 months was required. Progression was confirmed if at least one of the following criteria were met: an increase of at least 1.00 D in the steepest simulated keratometry reading (K-max); an increase in astigmatism determined by manifest subjective refraction of at least 1.00 D; an increase of 0.50 D in MRSE; or a 0.1 mm or more decrease in back optic zone radius of the best fitting contact lens. At the time of analysis for the 2008 report, 20 eyes had reached 1-year follow-up.

The 3-year results included 46 CXL and 48 control eyes. Last observation carried forward was used for 26 eyes, including 17 eyes from the control group with progressive disease that underwent compassionate use CXL or corneal transplantation. In the CXL group there was a flattening of Kmax by -1.03 D, compared with an increase in Kmax of 1.75 in the control group. One eye in the CXL group progressed by more than 2.0 D, compared with 19 eyes in the control group. Uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) improved in the CXL-treated eyes at 1, 2, and 3 years. In control eyes, UCVA was significantly reduced at 36 months and there was a trend of a decrease in BCVA (p=.10). The difference between the groups in UCVA was statistically significant. Follow-up is continuing through 5 years.

One-year outcomes of a crossover RCT were reported in 2011 from a U.S. Food and Drug Administration (FDA)â€'regulated multicenter trial of the UV-X system (IROC) (Hersh, 2011). Included in the study were 71 eyes of 58 patients 14 years of age or older with a diagnosis of progressive keratoconus or corneal ectasia, an inferior-superior ratio greater than 1.5 on topography mapping, and a BCVA worse than 20/20. If the cornea was thinner than 400 Âµm, hypotonic riboflavin was administered to swell the stroma. Patients were randomized to CXL or a control treatment consisting of 60 minutes of topical riboflavin alone with the light not turned on. Patients were aware of the treatment assignment, and the control patients crossed over to CXL treatment after the 3-month follow-up visit. With CXL, BCVA improved significantly at the 3-, 6-, and 12-month follow-up visits (from 20/45 at baseline to 20/34 at 12 months). There was a significant decrease in the maximum, average, flat, and steep K values during follow-up. Manifest astigmatism and MRSE did not change significantly. In the control group, there were no statistically significant changes in best corrected distance visual acuity (BCDVA), manifest astigmatism, MRSE, maximum, average or steep K values or corneal astigmatism at the 1-month and 3-month follow-up. A limitation of this trial is that the study design does not allow comparison of CXL and sham treatment over longer than 3 months.

In 2012, another publication from the randomized crossover trial described above reported on subjective visual function (Brooks, 2012). There were a total of 107 eyes (76 patients) with progressive keratoconus (n=71) or corneal ectasia (n=36). At 1 year after CXL, there were significant improvements in reading difficulty, diplopia, halo, and foreign body sensation in the keratoconus group. There was little to no correlation between the subjective and objective measures of vision and keratoconus progression. In addition to the limitation created by controls crossing over to active treatment after 3 months, there is a strong potential for bias in subjective measures when participants are not masked to treatment condition.

In 2010, Renesto et al reported results of a randomized trial that compared CXL versus 1 month of riboflavin eye drops in 39 eyes of 31 patients with keratoconus (Renesto, 2010). After 3 months, all patients received intrastromal corneal ring segments. Patients were evaluated at 1 and 3 months after treatment with CXL or riboflavin, and then at 1, 3, 6, 12, and 24 months after ICRS insertion. There was no significant difference between the 2 groups for UCVA, BCVA, or in 3 topographic parameters (flattest-K, steepest K, and average keratometry) throughout the 24-month follow-up. Coskunseven et al reported a within subject comparison of CXL in 38 eyes of 19 patients with progressive keratoconus in 2008. (Coskunseven, 2009). The eye of each patient that progressed more in the previous 6 months was treated with CXL, while the fellow (other) eye served as the control. At baseline, the treated eyes showed worse UCVA and BCVA, higher spherical equivalent refraction, cylinder, and maximal curvature (K-max), and lower pachymetry. Intraocular pressure (IOP) and endothelial cell count did not differ significantly between the treated and untreated eyes. At 9-months follow-up, CXL-treated eyes showed a significant decrease (less myopic) in spherical equivalent refraction (-1.03 D) cylinder (-1.04 D) and K-max (-1.57 D); these measures did not change significantly in untreated eyes (-0.03 D, -0.01 D, and +0.04 D, respectively). UCVA and BCVA increased in CXL-treated eyes (+0.06 and +0.10, respectively) and decreased in untreated eyes (-0.08 and -0.06, respectively). There was an increase in IOP from 9 to 11 mm Hg in CXL-treated eyes.

Uncontrolled Studies

In 2008, Raiskup-Wolf et al reported outcomes of 241 eyes (130 patients) treated with CXL, with a minimum of 6 monthsâ€™ follow-up (Raiskup-Wolf, 2008). This was out of a total of 488 eyes (272 patients) with progressive keratoconus and a corneal thickness of at least 400 Âµm treated at their center in Germany. Progression was indicated by either an increase in maximum K of 1.00 D in 1 year, patient report of deteriorating visual acuity, or the need for new contact lens fitting more than once in 2 years. Follow-up examinations were performed at 1, 6, and 12 months, and then annually. The mean follow-up was 26 months with a range of 12 months (n=142) to 6 years (n=5). In the first year (n=142), steepening (K-max) improved or remained stable in 86% of eyes, and BCVA improved by at least 1 line in 53% of the eyes. Three years after treatment (n=33), K-max improved by a mean of 2.57 D in 67% of eyes while BCVA improved by at least 1 line in 58% of eyes. This study is limited by the retrospective nature of the study and the low number of cases with extended follow-up.

Twelve-month results from 142 eyes treated with CXL from the French National Reference Center for Keratoconus were reported in 2011 (Asri, 2011). Inclusion criteria for this retrospective study were confirmed keratoconus, central corneal thickness greater than 400 Âµm, disease progression proven by previous central keratometry reports, and subjective loss of vision (loss of >2 lines in 1 year or keratometry increasing more than 1.0 D in 6 months or 2.0 D in 12 months). Stable visual acuity was defined as a 1-line change in BCVA, improvement was defined as a 2-line gain of BCVA, and failure was a 2-line loss in BCVA. Progression was defined as an increase of more than 1.0 D in K-max in 6 months or of more than 2.0 D in 12 months. Out of 142 eyes enrolled in the study, 6-month follow-up was available for 104 (73.2%), and 12-month follow-up was available for 64 (45.1%). At 12 months after treatment, the BCVA had stabilized in 31 of the 64 eyes (47.6%), improved in 26 eyes (40%) and decreased in 8 eyes (12%). Keratoconus progression had stopped in 42 eyes (68.8%), and the K-max value had decreased by more than 2.0 D in 13 eyes (21.3%). There was a 7% complication rate in the total sample, with 5 eyes (3.5% of 142 or 7.8% of 64) losing more than 2 Snellen lines of visual acuity. Indicators of failure were preoperative K-max greater than 58.0 D, age older than 35 years, and female gender. This retrospective study is also limited by the low percentage of patients available at 12-month follow-up.

A 2010 publication from the Siena Eye Cross Study reported a 52.4 month mean follow-up (range, 48-60 months) on their first 44 keratoconic eyes treated with CXL (Caporossi, 2010). Included in the study were 44 patients between 10 and 40 years of age with disease progression in the previous 6 months, minimum corneal thickness of 400 Âµm in the thinnest point, topographic mean K value less than 55 D, clear cornea by slit-lamp examination, and absence of eye infections, herpetic clinical history, autoimmune disease, and pregnancy. Follow-up evaluations were performed at 1, 2, 3, 6, 12, 24, 36, 48, and 60 months after CXL. Topographic analysis showed a mean K reading reduction of -1.96 D after 1 year, -2.12 D after 2 years, -2.24 D after 3 years, and -2.26 D after 4 years of follow-up. By comparison, in fellow eyes untreated for the first 24 months, the mean K value increased by 1.2 D at 1 year and 2.2 D at 2 years. In treated eyes, UCVA improved by a mean of 2.41 lines after 12 months, 2.75 lines after 24 months, 2.80 lines after 36 months, and 2.85 lines after 48 months. There was no significant decrease in endothelial cell density, central corneal thickness, or IOP over follow-up. Temporary side effects included stromal edema in the first 30 days (70% of patients) and temporary haze (9.8% of patients). No persistent side effects were observed.

A 2012 publication from the Siena CXL Pediatrics trial reported 12- to 36-month follow-up after CXL in 152 patients aged 18 years or younger with keratoconus progression (Caporossi, 2010). Visual acuity increased by an average of 0.15 Snellen lines, whereas a clinically relevant change is generally considered to be 2 Snellen lines.

Adverse Events

Reported adverse events are relatively uncommon, but precise rates of adverse events are not available because of the lack of large studies with long-term follow-up. Adverse events reported to date include corneal endothelial damage, stromal haze, corneal melt, keratitis, gaping of corneal incisions, and corneal scarring (Gkika, 2011; Gokhale, 2011; Abad, 2011).

Ongoing Clinical Trials
A search of online site ClinicalTrials.gov in February 2014 identified 30 open trials of corneal CXL. Some of the randomized controlled studies of CXL for keratoconus include:

- An industry-sponsored multicenter sham controlled trial of the KXL system with riboflavin (NCT01344187). The study will evaluate the change in maximum corneal curvature at 6 and 12 months after active and sham treatment. The study began August 2011, has completed enrollment with a target of 226 patients, and has a completion date of December 2014.
- A randomized comparison of 3 intensities with the KXL system (NCT01459679). The study began in 2012, has an estimated enrollment of 4000 patients, and a completion date of December 2014.
- A randomized comparison of CXL or sham in 130 patients with keratoconus (NCT00626717). The primary outcome measures are keratoconus progression and endothelial cell loss at 3 years. This study is listed as completed as of January 2013.
- A phase 3 trial of the Vedera KXS Microwave System combined with CXL compared with CXL alone (NCT01672814). The study has an estimated enrollment of 130 patients with completion expected August 2014.
- A phase 3 noninferiority trial comparing iontophoretic vs standard riboflavin for CXL (NCT01868620). The study has an estimated enrollment of 162 patients with completion expected in May 2016.
- A multicenter, randomized, placebo-controlled evaluation of the safety and efficacy of the KXL System with VibeX (Riboflavin Ophthalmic Solution vs. placebo) for CXL in eyes with keratoconus (NCT01972854). The study sponsor is Avedro. The study began in 2013 and has an estimated enrollment of 206 patients. Completion is expected in March 2016.
- A phase 3 randomized trial of CXL for the treatment of keratoconus and pellucid marginal degeneration (NCT01604135). The study is sponsored by university hospitals in Sweden and has an estimated enrollment of 200 patients. Completion is expected in May 2015.

Also identified on ClinicalTrials.gov is the German Corneal Cross-Linking Registry (NCT00560651). Goals of the registry are to gather long-term results of CXL, detect rare complications and side effects, and evaluate efficacy in a large number of patients. There is an estimated enrollment of 7500 patients with a study completion date of November 2012. The status of this study is unknown.

Summary
Corneal cross-linking (CXL) is a treatment for progressive keratoconus and other forms of corneal ectasia. There is evidence from a number of small randomized controlled trials (RCTs) that CXL leads to short-term improvements in visual acuity compared with untreated eyes, and results from 1 trial have reported that benefits are maintained at 2 to 3 yearsâ€™ follow-up. However, due to the variable natural history of keratoconus, there is a need for prospective RCTs with larger numbers of patients that are followed over many years to determine whether CXL improves longer-term outcomes. Several trials are ongoing, and results from these other trials 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 Food and Drug Administration (FDA) review for a humanitarian device exemption (HDE), no CXL devices have received FDA approval at this time.

Practice Guidelines and Position Statements
In 2013 the National Institute for Health and Care Excellence issued an Interventional Procedure Guideline (IPG 466)(NICE, 2013) that replaced the 2009 IPG 320. The new IPG now stratifies their recommendations for corneal CXL as follows:

â€œMost of the published evidence on photochemical corneal collagen cross-linkage (CXL) using riboflavin and ultravioletA (UVA) for keratoconus and keratectasia relates to the technique known as 'epithelium-off' CXL'. 'Epithelium-on (transepithelial) CXL' is a more recent technique and less evidence is available on its safety and efficacy. Either procedure (epithelium-off or epithelium-on CXL) can be combined with other interventions, and the evidence base for these combination procedures (known as 'CXL-plus') is also limited. Therefore, different recommendations apply to the variants of this procedure, as follows:

1.1 Current evidence on the safety and efficacy of epithelium-off CXL 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.

1.2 Current evidence on the safety and efficacy of epithelium-on (transepithelial) CXL, and the combination (CXL-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 researchâ€.

Information on corneal cross-linking and ongoing trials is provided by the National Keratoconus Foundation (National Keratoconus Foundation, 2014).

2015 Update

This policy was updated with a literature search conducted using the MEDLINE database through April 2015. The following is a summary of the key identified literature.

Data submitted to the FDA under the NDA for riboflavin ophthalmic solution/KXLÂ® came from 3 RCTs with a total sample size of 640 patients (U.S. Food and Drug Administration, 2015). Results from 1 of the trials were published in 2011 and 2012 (Hersh, 2011; Brooks, 2012). Each of the Phase III trials was a parallel group, open-label trial in patients with keratoconus or corneal ectasia due to LASIK or photorefractive keratectomy (PRK). Sham-control eyes were treated with a topical anesthetic and riboflavin solution (1 drop every 2 minutes for 30 minutes) but did not undergo epithelial debridement or have the UVA light source turned on. The primary outcome was a 1 diopter (D) difference in the mean change in K-max (progression of steepening) between the CXL and control groups at 12 months. Control patients could cross over to CXL at 3 months, and missing data were analyzed by last observation carried forward (LOCF). Ninety-nine percent of control patients had crossed over by 12 months. LOCF analysis is a conservative method of analysis in this situation, because it reduces the expected worsening over time in untreated patients. In the pooled analysis of patients with keratoconus, steepening worsened by 1.0 D in the control group and improved by 1.6 D in the CXL group, for a total difference between groups of 2.6 D. CXL resulted in either stabilization or improvement in K-max in 72% of keratoconus patients. In the sham control group, there was no statistically significant change in K-max. The mean improvement in best-corrected visual acuity (BCVA) was 5.6 letters following CXL compared with 2.0 letters for controls (p=0.009). Although this difference is not typically considered clinically significant, it is limited by the use of 3-month data for many of the patients in the control group which would minimize between-group differences over time. The proportion of patients who had a clinically significant 3-line or greater improvement in BCVA was 19.4% for the CXL-treated patients and 8.1% for controls. Treatment-related adverse events were generally transient, mild, and expected based on the epithelial debridement and corneal remodeling.

In 2015, the same group published 10 year follow-up of CXL treatment in 34 eyes (24 patients) with progressive keratoconus (Raiskup, 2015). Mean patient age at the time of treatment was 28 years (range: 14 to 42). Corneal steepening improved slightly between baseline and 10 year follow-up (p<0.001), while corrected distance visual acuity (CDVA) improved by 0.14 logMAR (p=0.002). Two eyes had repeat CXL, one at 5 years and one at 10 years, without adverse sequelae. One of the 34 eyes treated developed a permanent corneal scar.

2017 Update

A literature search conducted through June 2017 did not reveal any new information that would prompt a change in the coverage statement. The key identified literature is summarized below.

Best Spectacle-Corrected Visual Acuity

The visual acuity outcomes as assessed by mean improvement in best spectacle-corrected visual acuity (BSCVA) and responder analysis (gain of â‰¥15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] is considered clinically meaningful) are summarized in Tables 2 and 3, respectively. Statistical procedures to control for type I error for multiple comparisons were not described in either the sponsor\l " (Avedro, 2015) or in FDA documents (FDA, 2017; FDA, 2015) Therefore, these results should not be used for statistical inference. In the pooled analysis of the observed data, the mean change in sham-control patients for progressive keratoconus at 6 months was +1.1 letter (n=38) compared to +5.8 (n=96) for CXL-treated patients, yielding a difference of 4.7 letters in favor of CXL treatment. Respective numbers for patients with ectasia were -0.4 letters (n=88) versus +4 letters (n=91), yielding a difference of 4.4 letters in favor of CXL treatment.

McAnena and colleagues reported results of a systematic review and a meta-analysis assessing the efficacy of CXL treatment for keratoconus in pediatric patients (McAnena, 2016). A total of 13 articles, published between May 2011 and December 2014, examining 490 eyes of 401 patients (mean age, 15.25 years), were included in the meta-analysis. Bias assessment of individual studies was not included. Reviewers reported a significant improvement in BCVA at 6 months (standardized mean difference [SMD], -0.66; 95% confidence interval [CI], -1.22 to -0.11; p=0.02), which was maintained at 1 year (SMD = -0.69; 95% CI, -1.15 to -0.22; p<0.01). Two-year data were available for 3 studies (n=131 eyes) and the improvement in BCVA remained significant (SMD= -1.03; 95% CI, -2 to -0.06; p=0.04).

Uncontrolled Studies

Longer term follow-up is being reported from Europe, where corneal CXL has been performed for a greater number of years. Indications for treatment typically include progression of steepening (increase in Kmax by at least 1 D in 1 year), deteriorating visual acuity, or the need to be fitted for new contact lenses more than once in 2 years. The largest and longest series to date are described next.

Padmanabhan and colleagues retrospectively analyzed 377 eyes of 336 patients (mean age, 15 years) who underwent CXL for progressive keratoconus (Padmanabhan, 2016). There was significant improvement in mean BSCVA from 0.33 to 0.27 logMAR (p<0.05). The authors found that the benefits of CXL in stabilizing keratoconus were maintained for more than 2 years in most pediatric eyes.

In 2008, Raiskup-Wolf and colleagues reported outcomes of 241 eyes (272 patients) treated with CXL, with a minimum of 6 months of follow-up (Raiskup-Wolf, 2008). Follow-up examinations were performed at 1, 6, and 12 months, and then annually. Mean follow-up was 26 months, with a range of 12 months (n=142) to 6 years (n=5). In the first year (n=142), steepening (Kmax) improved or remained stable in 86% of eyes, and BCVA improved by at least 1 line in 53% of the eyes.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in July 2017 did not identify any additional ongoing or unpublished trials that would likely influence this review.

2018 Update

A literature search was conducted through July 2018. There was no new information identified that would prompt a change in the coverage statement. The key identified literature is summarized below.

Other Randomized Controlled Trials

Keratoconus

Hersh et al analyzed 205 patients who had keratoconus treated with CXL (n=102) or a sham procedure (n=103) in a phase 3, prospective, randomized, controlled trial (Hersh, 2017). At 1 year, those in the treatment group had a significant decrease in Kmax score (1.6) compared with baseline, while the control group saw an increase in Kmax (1.0); the between-group difference in Kmax change was 2.6 D (p<0.001). Mean corrected distance visual acuity (CDVA) improved significantly more in the treatment group (5.7 logMAR) than in the control group (2.2 log MAR; between-group difference, 3.5 logMAR;
p<0.01). A similar finding, though statistically insignificant, was observed for mean uncorrected distance visual acuity, with the treatment group improving by 4.4 logMAR, compared with the control group (2.6 logMAR; between-group difference, 1.8 logMAR). Endothelial cell count did not change significantly from baseline to 1 year in either group. The trial was limited in that patients in the control group were allowed to switch to CXL treatment after 3 months; thus, their data were imputed based on the LOCF method. Also, in the control group, patients did not undergo removal of their epithelium.

Renesto et al reported on 2-year results of a randomized trial that compared CXL with 1 month of riboflavin eye drops in 39 eyes of 31 patients with keratoconus (Renesto, 2010). After 3 months, all patients received intrastromal corneal ring segments (see evidence review 9.03.14). Patients were evaluated at 1 and 3 months after treatment with CXL or riboflavin, and then at 1, 3, 6, 12, and 24 months after intrastromal corneal ring segments insertion. There were no significant differences between the 2 groups for UCVA, BCVA, or in 3 topographic parameters (flattest K, steepest K, and average keratometry) throughout the 24-month follow-up.

Uncontrolled Studies

Keratoconus

Longer term follow-up is being reported from Europe, where corneal CXL has been performed for a greater number of years. Indications for treatment typically include progression of steepening (increase in Kmax by at least 1 D in 1 year), deteriorating visual acuity, or the need to be fitted for new contact lenses more than once in 2 years. The largest and longest series to date are described next.

Toprak et al retrospectively analyzed 29 eyes from pediatric patients (age range, 10-17 years) whose progressive keratoconus was treated with unilateral CXL treatment (Toprak, 2017). From baseline to 2-year follow-up, there was a significant decrease in mean CDVA (0.34 logMAR to 0.13 logMAR; p<0.001). Maximum keratometry (Kmax) measures decreased from baseline 54.65 to 53.25 at 2 years (p=0.034), while anterior chamber parameters, corneal thickness, and corneal volume were not significantly affected by CXL after 2 years (p>0.05). Several parameters of the Scheimpflug imaging system were improved following CXL treatment: index of surface variance decreased from 69.75 at baseline to 62.95 at 2 years (p=0.004); keratoconus index decreased from 1.16 (p=0.001); center keratoconus index decreased from 1.05 to 1.04 (p=0.004); and index of height decentration decreased from 0.056 to 0.042 (p=0.001). The radius of minimum curvature (Rmin) increased significantly from baseline to 2 years (6.21 to 6.36; p=0.007), although 2 other indices (indices of height and vertical asymmetry) did not change significantly. The authors noted that follow-up beyond 2 years is required to make long-term assessments of CXL as a treatment for keratoconus, but concluded that their results seemed favorable for postoperative outcomes.

Badawi et al published a prospective nonrandomized observational study of accelerated CXL to treat pediatric patients with keratoconus (Badawi, 2017). Of the 25 patients (33 eyes) enrolled, 80% were male, and most patients (n=17) received unilateral CXL, administered with VibeX Rapid solution and Vega CBM X-Linker. The groupâ€™s mean unaided and aided visual acuity were significantly improved at all time points (3, 6, and 12 months): at 12-month follow-up, the mean unaided visual acuity score was 0.34, which was a significant decrease compared with preoperative mean score (0.54; p<0.001). For aided visual acuity, there was a similar decrease from preoperative (0.36) to 12-month (0.17) time points (p<0.001). Mean corneal astigmatism values also decreased significantly (preoperative 2.4 D decreased to 2.01 D at 12 months; p<0.001). The mean Kmax showed an average flattening of 1.2 D in 1 year (49.12 D decreasing to 47.9 D; p<0.001); the authors reported significant improvements in other measures such as central pachymetry, maximum anterior elevation, average progression indices, and Q values. A limitation of the study was the slight increase observed in posterior surface elevation, which, contrary to other study measures, showed no significant positive effect 12 months after accelerated CXL (p=0.9). Advising further study of the procedure, the authors noted that the unusual result might be accounted for by the choice of Pentacam as a corneal analysis tool because there might have been corneal artifacts present during evaluation.

Knutsson et al published a prospective cohort study of 43 patients (52 eyes) between the ages of 12 and 17 who underwent CXL as a treatment for keratoconus in 1 or both eyes (Knutsson, 2018). Two-year outcomes were reported for all patients, although longer-term (up to 7 years) follow-up was available for 21 eyes. At 2 years, overall mean Kmax decreased from 59.30 Â± 7.08 to 57.07 Â± 6.46 (p<0.001), and overall mean UCVA and BSCVA decreased, although not significantly. Additional analyses were conducted of patients whose eyes had Kmax values of 60 D or greater (n=25), compared with those whose keratometry was less severe (<60 D). As with the overall findings, mean Kmax for both cohorts were significantly decreased for both cohorts, while neither UCVA nor BSCVA measures changed significantly at 1 or 2 years. In patients with advanced keratoconus, mean Kmax decreased from 64.94 (95% CI, 62.94 to 66.94) to 62.25 (95% CI, 60.55 to 63.95) at 2 years (p<0.001); for the less-advanced cohort, mean Kmax decreased from 53.88 (95% CI, 52.48 to 55.28) at baseline to 52.08 (95% CI, 50.68 to 53.48) at 2 years (p<0.001). While most findings were favorable for the efficacy of CXL in treating even severe keratometry, the authors noted that the study was limited by the use of 2 pachymetric measurement techniques (optical coherence

tomography and ultrasound) rather than a single technique across the study. Further, the lack of full long-term data for all patients limited the study to reporting only 2-year outcomes.

CPT/HCPCS:

0402T	Collagen cross-linking of cornea (including removal of the corneal epithelium and intraoperative pachymetry when performed)
66999	Unlisted procedure, anterior segment of eye

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Group specific policy will supersede this policy when applicable. This policy does not apply to the Wal-Mart Associates Group Health Plan participants or to the Tyson Group Health Plan participants.