Corneal collagen cross-linking (CXL) is used to treat corneal ectasia from progressive conditions such as keratoconus, other corneal degeneration or a complication following keratorefractive surgery. Corneal ectasia is a noninflammatory condition that causes progressive corneal steepening and thinning and are associated with decreased uncorrected visual acuity. There are 2 protocols for this procedure. Epithelium-off CXL (also known as “epi-off”) stiffens the cornea through a combination of exposure to ultraviolet light and eye drops containing riboflavin (vitamin B2). Debridement of the epithelium is done first followed by the application of riboflavin eye drops at frequent intervals for about half an hour to saturate the corneal stroma. Epithelium-on CXL (also known as “epi-on” or transepithelial), the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed. After applying riboflavin, the cornea is exposed to UV light, causing the collagen fibrils to interconnect, thus increasing corneal rigidity. Currently, the only CXL treatment approved by the Food and Drug Administration (FDA) is the epithelium-off method. CXL is generally not performed in patients with active or history of herpes simplex virus (HSV) keratitis, thin corneas, or corneal hydrops.

U.S. Food and Drug Administration FDA: Avedro Inc., received approval from the FDA in April of 2016 for Photrex Viscous, Photrex and the KXL System. Photrex Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146% and Photrex (riboflavin 5'-phosphate ophthalmic solution) 0.146% are photoenhancers indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus.
**RECOMMENDATION**

Corneal Collagen Cross-Linking is considered experimental, investigational and unproven due to insufficient evidence in the peer reviewed medical literature and may not be authorized.

**SUMMARY OF MEDICAL EVIDENCE**

The peer reviewed medical evidence for corneal CXL in individuals who have keratoconus includes randomized controlled trials (RCTs), prospective trials with historical controls, prospective comparative cohort studies, retrospective comparative cohort studies and systematic reviews. Outcomes reported are change in disease status, functional outcomes, and treatment-related morbidity. Evidence from the available studies suggests that 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 CXL does not seem to impact measures of refraction. 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.

Two meta-analyses and a Cochrane review analyzed RCTs comparing Conventional Dresden Protocol (C-CXL) versus no treatment and evaluated 5 RCTs that reported significant improvements in best spectacle corrected visual acuity (BSCVA) among patients treated with C-CXL compared with untreated eyes. There were no significant differences between groups for changes in corneal thickness and cylindrical refraction. Maximum keratometry (Kmax), uncorrected distance visual acuity (UDVA), and spherical equivalent (SE) refraction were not evaluated in the meta-analysis due to substantial heterogeneity (I² > 50%) in these outcomes between RCTs. A 2015 meta-analysis evaluated 6 RCTs and reported significant decreases in keratometry measures and improved BSCVA in the C-CXL treatment group; however, the meta-analysis included 1 RCT with only 3 months of postoperative follow-up and authors did not adjust the calculated outcomes for the postoperative time period. In addition, significant heterogeneity was detected between studies in the keratometry outcome measures. Finally, a 2015 Cochrane systematic review analyzed 3 RCTs evaluating C-CXL versus no treatment in adults with keratoconus. Authors found that, on average, C-CXL-treated eyes had flatter corneas and better UDVA than untreated eyes at 1 year. Findings were inconsistent regarding corneal thickness, and no studies evaluated quality of life. The authors concluded that the evidence was of very-low quality because of problems in the way the studies were done, including sample size, imprecision, and indirectness.

A prospective randomized, controlled trial reported the refractive, topographic, and clinical outcomes 3 years after corneal collagen cross-linking (CXL) in eyes with progressive keratoconus. One hundred eyes with progressive keratoconus were randomized into the CXL treatment or control groups. The primary outcome measure was the maximum simulated keratometry value (Kmax). Other outcome measures were uncorrected visual acuity (UCVA; measured in logarithm of the minimum angle of resolution [logMAR] units), best spectacle-corrected visual acuity (BSCVA; measured in logMAR units), sphere and cylinder on subjective refraction, spherical equivalent, minimum simulated keratometry value, corneal thickness at the thinnest point,
endothelial cell density, and intraocular pressure. The results from 48 control and 46 treated eyes reported that in control eyes, Kmax increased by a mean of 1.20±0.28 diopters (D), 1.70±0.36 D, and 1.75±0.38 D at 12, 24, and 36 months, respectively (all P <0.001). In treated eyes, Kmax flattened by -0.72±0.15 D, -0.96±0.16 D, and -1.03±0.19 D at 12, 24, and 36 months, respectively (all P <0.001). The mean change in UCVA in the control group was +0.10±0.04 logMAR (P = 0.034) at 36 months. In the treatment group, both UCVA (-0.15±0.06 logMAR; P = 0.009) and BSCVA (-0.09±0.03 logMAR; P = 0.006) improved at 36 months. There was a significant reduction in corneal thickness measured using computerized videokeratography in both groups at 36 months (control group: -17.01±3.63 µm, P <0.001; treatment group: -19.52±5.06 µm, P <0.001) that was not observed in the treatment group using the manual pachymeter (treatment group: +5.86±4.30 µm, P = 0.181). The manifest cylinder increased by 1.17±0.49 D (P = 0.020) in the control group at 36 months. There were 2 eyes with minor complications that did not affect the final visual acuity. The authors concluded that at 36 months, there was a sustained improvement in Kmax, UCVA, and BSCVA after CXL, whereas eyes in the control group demonstrated further progression.  

**Professional Society Guidelines**  

The American Academy of Ophthalmology PPP 2013 states that “collagen cross-linking has the potential to reduce the risk of progressive ectasia (particularly in its early stages) and stabilize the corneal contour. This is the case particularly in mild to moderate keratoconus, and it may also hold promise in cases of corneal ectasia occurring after keratorefractive surgery. The use of corneal mapping and the use of newer contact lens technologies may provide an alternative to surgery for treatment of corneal ectasia. Current CXL protocols require either the removal of the epithelium or exposure of the intact epithelium to agents that increase the permeability of the cell layer, followed by the application of topical riboflavin and UV-A treatment.” The evidence for this recommendation is grade II defined as Insufficient or Discretionary.  

National Institute for Health and Clinical Excellence (NICE) IPG466 states that “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. NICE encourages further research into CXL using riboflavin and UVA for keratoconus and keratectasia, especially epithelium-on (transepithelial) CXL and the combination (CXL-plus) procedures. Details of the techniques used should be clearly described. Reported outcomes should include visual acuity, corneal topography and quality of life. Data on long-term outcomes for all types of CXL using riboflavin and UVA for keratoconus and keratectasia would be useful, specifically data about prevention of progression to corneal transplantation and about repeat procedures and their efficacy.”  

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<td>Collagen cross-linking of cornea including removal of the corneal epithelium and intraoperative pachymetry when performed</td>
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REFERENCES

Government Agency

Professional Society Guidelines and other Publications

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Other Resources

32. Hayes. Winifred Hayes Inc. Lansdale, PA.
   - Wayman LL. Keratoconus. 2018
34. Advanced Medical Review (AMR): Policy reviewed by practicing MD board certified in Ophthalmology. 10/29/18

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