

MEDICAL POLICY		Eye: Corneal Collagen Cross-Linking (All Lines of Business Except Medicare)	
Effective Date: 06/01/2020		Section: MED	Policy No: 431
 <div style="text-align: right;">6/1/2020</div>		Medical Policy Committee Approved Date: 10/18; 12/18; 5/19; 05/2020	
		Medical Officer	Date

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

All lines of business except Medicare

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

- I. Conventional collagen cross-linking (C-CXL, epithelium-off) using riboflavin and ultraviolet A may be considered **medically necessary** for the treatment of progressive keratoconus or corneal ectasia following refractive surgery when **all** of the following criteria are met (A. – G.):
 - A. Patient is between 14 and 65 years of age; **and**
 - B. Axial topography pattern consistent with keratoconus or corneal ectasia; **and**
 - C. An inferior–superior ratio greater than 1.5 on topography mapping, **and**
 - D. Corrected distance visual acuity (CDVA) worse than 20/20, **and**
 - E. A diagnosis of progressive keratoconus or LASIK-induced or photorefractive keratectomy (PRK)-induced ectasia, defined as **one or more** of the following changes:

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1. An increase of 1.00 diopter (D) or more in the steepest keratometry (K) measurement, **or**
 2. An increase of 1.00 D or more in manifest cylinder, **or**
 3. An increase of 0.50 D or more in manifest refraction spherical equivalent (MRSE); **or**
 4. A 1.0 D or a 0.1 mm or more decrease in the back optic zone radius of contact lens wearers, where other information is not available; **and**
- F. Conservative treatment such as spectacle correction or use of rigid contact lenses has failed; **and**
- G. None of the following exclusions are present:
1. Previous corneal surgery (other than refractive surgery), **or**
 2. Corneal pachymetry less than 300 μm , **or**
 3. History of any **one or more** of the following:
 - a. Chemical injury or burns, **or**
 - b. Delayed epithelial healing, **or**
 - c. Severe infections, **or**
 - d. Other corneal or ocular surface disorders; **or**
- II. Collagen cross-linking is considered **investigational and not covered** when criterion I above is not met, including but not limited to:
- A. The use of other CXL techniques and protocols, including but not limited to:
1. Transepithelial collagen cross-linking (Epithelium-on, T-CXL).
 2. Accelerated CXL (A-CXL).
 3. Partial epithelium-removal CXL (P-CXL).
 4. Topography-guided CXL (TG-CXL).
- B. When CXL is used in combination with other procedures, also known as CXL-plus (e.g., intrastromal corneal ring segments, PRK or phakic intra-ocular lens implantation).
- C. Treatment of other corneal indications, including, but not limited to infectious keratitis.

Link to [Policy Summary](#)

BILLING GUIDELINES

Corneal collagen cross-linking (CXL) maybe be requested in combination with other procedures, such as phototherapeutic keratectomy (PTK). These combination procedures are considered investigational per this medical policy. Therefore, when the HCPCS code for PTK (S0812) is billed with 0402T, both codes should deny as investigational.

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CPT/HCPCS CODES

All Lines of Business Except Medicare	
Prior Authorization Required	
0402T	Collagen cross-linking of cornea, (including removal of the corneal epithelium and intraoperative pachymetry, when performed) (Report medication separately)
J2787	Riboflavin 5'-phosphate, ophthalmic solution, up to 3 mL
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then prior-authorization is required.	
66999	Unlisted procedure, anterior segment of eye

DESCRIPTION

Corneal Collagen Cross-Linking (CXL)

Corneal collagen cross-linking (CXL), also simply known as corneal cross-linking, is a relatively new technique currently being investigated as a treatment to slow the progression of corneal ectasias, including keratoconus and postkeratorefractive ectasia; as well as other corneal conditions.

CXL is thought to increase the biomechanical strength of collagen fibrils of the cornea through the application of riboflavin (vitamin B2) eye drops, which are absorbed by the corneal stroma. After the application of the drops, ultraviolet A (UVA) radiation is used to trigger a photochemical reaction that changes the cross-links between and within collagen fibers in the stroma. This is believed to strengthen and increase the biomechanical stiffness of the stroma, thereby flattening the steepened cornea into a more normal shape to improve vision.

Different approaches to remove or penetrate the corneal epithelium and different UVA light intensities have given rise to a variety of CXL approaches:

- *Conventional CXL (C-CXL), also known as “epithelium off”*: C-CXL involves removing the epithelium completely, after which riboflavin drops are applied to the cornea and the UVA irradiation is administered for 30 minutes.
- *Accelerated CXL (A-CXL)*: A-CXL administers a similar UVA dose (fluence) to C-CXL, but in a shorter amount of time (10 minutes) by increasing the fluence rate or irradiance.
- *Transepithelial CXL (T-CXL), also known as “epithelium on”*: T-CXL is performed without epithelial removal in an effort to reduce patient discomfort and possibly lower the risk of infection compared with C-CXL. However, reduced absorption of riboflavin has been reported in the T-CXL approach.
- *Partial Epithelium-Removal CXL (P-CXL)*: P-CXL is performed by partially removing the epithelium in an effort to reduce corneal damage and promote faster reepithelialization. However, as with T-CXL,

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reduced riboflavin absorption has been reported.

- *Topography-Guided CXL (TG-CXL)*: TG-CXL is performed using a customized, patient-specific UVA irradiation pattern based on circular zones over the keratoconic cone region of the cornea. These zones are centered on the maximum posterior elevation and receive varying amounts of energy depending on the severity of the curvature, with higher levels of energy being delivered to the innermost zones compared with outermost zones.
- *CXL combined with other procedures (CXL-plus)*: CXL-plus is the term used when either C-CXL or T-CXL are combined with other interventions, including but not limited to intrastromal corneal ring segments, photorefractive keratectomy (PRK) or phakic intra-ocular lens implantation.

Corneal Ectasia

According to the American Academy of Ophthalmology (AAO), “corneal ectasia is a noninflammatory condition, the hallmark of which is progressive corneal steepening and thinning.”¹ As a result, the cornea bulges outward and progressively develops a conical shape, which prevents light entering the eye from focusing directly on the retina, resulting in irregular astigmatism and progressive myopia or visual loss. “Corneal ectasias are associated with decreased uncorrected visual acuity (UCVA), an increase in ocular aberrations, and often a loss of best-corrected distance visual acuity (BCVA). Corneal ectasias can result in significant ocular morbidity and may require surgical intervention. Types of corneal ectasia include keratoconus, postkeratorefractive ectasia, pellucid marginal degeneration, keratoglobus, and wound ectasia after penetrating keratoplasty (PK).”

The clinical objectives for treating corneal ectasia are to understand appropriate surgical and non-surgical treatment options and to improve and/or prevent loss of visual function.

Alternative Treatment Options

Apart from CXL, alternative treatment options for corneal ectasias include corrective lenses, gas-permeable contact lenses, and intraocular lenses. However, many patients cannot tolerate the rigid lenses. Alternatively, minimally invasive intracorneal ring segment implantation (e.g. Intacs, Keraring, Ferrara ring, Myoring) is another treatment option. However, the initial effects of the rings are reported to regress with time. Ablative procedures including photorefractive keratectomy, phototherapy keratectomy, lamellar keratoplasty, and penetrating keratoplasty are also an option. However, none of these treatments change the course of the disease, and patients with advanced disease often need corneal transplantation.

Keratoconus

Keratoconus is the most common corneal ectasia, with prevalence reporting between estimates 760 to 3300 cases per 100,000 people. Naturally occurring keratoconus typically begins in the second decade of life and progresses until about age 40. It is a predominantly bilateral form of corneal degeneration, but may be asymmetrical as well. In keratoconus, collagen fibers within the cornea naturally weaken and the cornea can no longer maintain the normal round shape, causing loss of visual acuity.

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Postkeratorefractive Ectasia

Postkeratorefractive ectasia, also known as keratectasia, is a type of secondary corneal ectasia that has been associated with refractive surgery, particularly laser-assisted in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK). The incidence is rare, with between 0.02% and 0.6% of LASIK patients developing the condition. Postkeratorefractive ectasia may occur within a week of surgery or several years later, but the majority of cases occur within two years post-LASIK. Although it has not been clearly established, post-surgery ectasia is hypothesized to develop in patients whose cornea is already weak and predisposed to ectasia. Conversely, it may occur when a normal cornea is weakened by surgery to a point of instability.

REVIEW OF EVIDENCE

Currently, the only corneal collagen cross-linking (CXL) system with FDA approval is the KXL[®] System (Avedro). The KXL[®] System is only indicated for use with the conventional “epithelium-off” C-CXL protocol and only as a treatment for keratoconus or corneal ectasia following refractive surgery. The KXL[®] System is not approved for use with any other CXL technique or protocol, including but not limited to:

- Transepithelial collagen cross-linking (Epithelium-on, T-CXL)
- Accelerated CXL (A-CXL)
- Partial epithelium-removal CXL (P-CXL)
- Topography-guided CXL (TG-CXL)
- CXL combined with another procedure (CXL-plus)

The health plan considers devices that are not FDA-approved to be investigational and not covered. The following evidence review is only focused on FDA-approved devices. In addition, evidence reviews for indications not covered by the FDA (e.g., infectious keratitis) were conducted at this time.

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of conventional corneal collagen cross-linking (C-CXL) as a treatment for keratoconus or corneal ectasia following refractive surgery. Below is a summary of the available evidence identified through April of 2012.

In 2018, ECRI published a rapid response review of CXL for treating keratoconus and corneal ectasia, which was last updated in February 2019.² Given the large body of evidence, ECRI included systematic reviews (SRs) with meta-analysis and randomized controlled trials (RCTs) with 30 or greater patients in their review. Included studies assessed 2,000+ eyes. Overall, ECRI reports the evidence is favorable based on one recent SR and three RCTs not included in the SR, which found CXL-treated patients had improved visual acuity one year after treatment. Adverse event reports have been low. Long term data are still lacking; the ECRI authors concluded that longer term RCTs are still warranted.

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Keratoconus

Systematic Reviews

In recent years, a large number of systematic reviews have been published on the efficacy of C-CXL for the treatment of keratoconus. The summary of the reviews below is organized by comparator group.

Two systematic reviews have assessed the efficacy of CXL for the treatment of keratoconus without specifically comparing it to another treatment. These reviews included large numbers of randomized and nonrandomized studies and have reported one or more of the following significant improvements among patients treated with C-CXL.^{3,4}

- improved visual acuity, as measured by uncorrected distance visual acuity (UDVA) and/or best-spectacle-corrected visual acuity (BSCVA)
- improved topography parameters:
 - reduced central corneal thickness (CCT)
 - improved refractive cylinder
 - improvements in other topography readings
- decreased endothelial cell density

In addition, in 2016, McAnena et al. published a systematic review that evaluated C-CXL in pediatric patients (aged 18 years or younger), including nine studies.⁵ The review reported improved UDVA and BSCVA and stable corneal curvature (as measured by maximum keratometry [Kmax]) at one-year post-procedure. They concluded that C-CXL may be effective in halting progression of keratoconus in pediatric patients.

Two meta-analyses and a Cochrane review analyzed a total of five RCTs comparing C-CXL versus no treatment, and reported one or more of the following significant improvements among patients treated with C-CXL compared with untreated eyes:⁶⁻⁸

- improved corrected visual acuity, as measured by BSCVA
- improved topography parameters: reduced corneal curvature, as measured by a decrease in maximum keratometry (Kmax)

Four meta-analyses have compared C-CXL with modified CXL techniques (A-CXL or T-CXL) and reported one or more of the following significant improvements among patients treated with C-CXL compared with modified techniques:⁹⁻¹²

- reduced corneal curvature (Kmax)
- delayed deterioration of Kmax
- improved minimum keratometry (minK)
- greater reduction in mean keratometry (mean K)
- improved demarcation line depth

In 2018, Hayes conducted a general comparative effectiveness review on CXL for treatment of keratoconus, including nine randomized controlled trials (RCTs).¹³ The review was last updated in 2019. Despite the “C” rating given to the use of C-CXL for the treatment of progressive keratoconus in adolescent and adult patients compared with no treatment or sham treatment, the review did note that there is a moderately sized body of low-quality evidence that suggests some positive results regarding the benefits of C-CXL. The Hayes review also included eight systematic reviews that evaluated C-CXL for the treatment of keratoconus that are summarized above.³⁻¹⁰

Randomized Controlled Trials (RCTs)

No RCTs evaluating CXL were identified after the publication of the Hayes review.

Corneal Ectasia Following Refractive Surgery

Systematic Reviews

In 2017, a systematic review was published that assessed the efficacy of CXL for the treatment of post-laser vision correction ectasia, including seven studies (118 patients, 140 eyes) treated with CXL for progressive ectasia after laser-assisted in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK).¹⁴ The follow-up time ranged from 12 to 62 months and the review reported significantly improved corrected distant visual acuity (CDVA) in patients who underwent CXL. Of note, the five RCTs included in the review were all small in sample size and conducted on patient cohorts outside of the United States.

Randomized Controlled Trials

Outside of the United States there have been a number of RCTs published by the same group, using the same patient population, simply reporting various one-year outcomes of CXL for the treatment of corneal ectasia after previous refractive surgery.¹⁵⁻¹⁸ Collectively, these publications reported significant improvements in the following:

- corneal topography, including improvements in the index of surface variance, index of vertical asymmetry, keratoconus index, and minimum radius of curvature.
- improved visual acuity measures, including UDVA and CDVA.

This same group (Hersh et al. 2017) published the results of their first U.S. trial, the pivotal trial that was used as the basis for the FDA approval of the Avedro KXL System for this indication.¹⁹ The authors published one-year results of the prospective multicenter RCT, including 179 patients randomized to either standard C-CXL or a sham control where riboflavin drops were applied without removal of the epithelium.¹⁹ In the C-CXL treatment group, Kmax decreased by 0.7 diopters (D) from baseline to one-year, whereas there was continued progression of corneal steepening in the control group (1.3 D difference between treatment and control, $P < 0.0001$). In the treatment group, the Kmax value decreased by 2.0 D or more in 14 eyes (18%) and increased by 2.0 D or more in three eyes (4%). Both the CDVA and the UDVA improved significantly in the C-CXL group. The authors concluded the C-CXL “was effective in improving the maximum K value, CDVA, and UDVA in eyes with corneal ectasia one year after treatment, with an excellent safety profile.”

CLINICAL PRACTICE GUIDELINES

American Academy of Ophthalmology (AAO)

In 2018, the AAO published an updated Preferred Practice Guideline pertaining to corneal ectasia.²⁰ In the highlights and recommendations for care, the AAO stated that CXL, “reduces the risk of progressive ectasia in patients with keratoconus (particularly in its early stages) and stabilizes the corneal. It also stabilizes cases of corneal ectasia occurring after keratorefractive surgery.” The guideline includes an extensive section on corneal cross-linking with indications, technique options, outcomes, contraindications, complications, and varying combination techniques.

National Institute for Health and Care Excellence (NICE)

In 2013, NICE published an interventional procedures guidance on photochemical corneal collagen cross-linkage using riboflavin and UVA for keratoconus and keratectasia.²¹ NICE noted that the majority of evidence focused on the epithelium-off (C-CXL) approach as a treatment for keratoconus and corneal ectasia. Transepithelial CXL (T-CXL, epithelium-on) procedure had considerably less evidence. In addition, “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.”

The NICE guidance recommended the following:

- “Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia is adequate in quality and quantity.
- 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.
- Patient selection for these procedures should include assessment of corneal thickness and consideration of the likelihood of disease progression.
- The procedures should only be carried out by ophthalmologists with expertise in managing corneal disease and specific training in the use of UV light or by appropriately trained staff under their supervision.”

POLICY SUMMARY

The evidence for the use of conventional epithelium-off corneal collagen cross-linking (C-CXL) for the treatment of keratoconus and post-laser vision correction ectasia has limitations, including a small number of studies reporting long-term follow-up. However, C-CXL appears to improve visual acuity and corneal curvature for a moderate amount of time (one- to three- years), thereby postponing corneal transplantation. Based on this, and the indications outlined in the FDA labelling, the evidence of safety and efficacy of C-CXL for FDA-approved indications is sufficient. In addition, current guidelines published by the National Institute for Health and Care Excellence (NICE) support the use of C-CXL for keratoconus and post-laser vision correction ectasia.

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The only FDA-approved system for CXL is the KXL[®] System. This system is only indicated for use with the conventional “epithelium-off” C-CXL protocol and only as a treatment for keratoconus or corneal ectasia following refractive surgery. Based on the health plan’s definitions, other indications (e.g., infectious keratitis, corneal ulcers) and other CXL protocols (e.g. T-CXL, A-CXL, CXL-plus) not approved by the FDA are considered investigational and not covered. In addition, current guidelines published by the National Institute for Health and Care Excellence (NICE) do not support the use of epithelium-on transepithelial (T-CXL) for keratoconus and post-laser vision correction ectasia. NICE guidelines do not address any other CXL protocol.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

U.S .Food & Drug Administration (FDA)

In 2016, PHOTREXA[®] VISCOUS and PHOTREXA[®] were approved and are indicated for use in corneal collagen cross-linking in combination with the KXL[™] System (NDA #203324) for the treatment of progressive keratoconus and corneal ectasia following refractive surgery.²²

PHOTREXA[®] is a 0.146% riboflavin 5'-phosphate ophthalmic solution), while PHOTREXA[®] VISCOUS is a 0.146% riboflavin 5'-phosphate in 20% dextran ophthalmic solution. Both solutions are for topical ophthalmic use and are only approved for use with the Avedro with the KXL[™] System, which is the company’s specific UVA irradiation device.

The Dosage and Administration” section of the FDA label indicates usage only of the conventional “epithelium-off” CXL protocol (C-CXL). The KXL[®] system has not been approved for the use with any other protocol (e.g., transepithelial “epithelium-on”) or for other indications (e.g., infectious keratitis, corneal ulcers).

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Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

REFERENCES

1. American Academy of Ophthalmology (AAO) Corneal / External Disease Panel. Preferred Practice Pattern® Guideline. Corneal Ectasia. 2013. <https://www.aao.org/preferred-practice-pattern/corneal-ectasia-ppp--2013>. Accessed 04/23/2020.
2. ECRI. Custom Rapid Responses - Guidance. Corneal Collagen Cross-linking for Treating Keratoconus and Corneal Ectasia. Published: 1/10/2018. Updated: 02/12/2019. <https://www.ecri.org/components/Hotline/Pages/25708.aspx?tab=2>. Accessed 04/23/2020.
3. Chunyu T, Xiujun P, Zhengjun F, Xia Z, Feihu Z. Corneal collagen cross-linking in keratoconus: a systematic review and meta-analysis. *Sci Rep*. 2014;4:5652. <https://www.ncbi.nlm.nih.gov/pubmed/25007895>
4. Meiri Z, Keren S, Rosenblatt A, Sarig T, Shenhav L, Varssano D. Efficacy of Corneal Collagen Cross-Linking for the Treatment of Keratoconus: A Systematic Review and Meta-Analysis. *Cornea*. 2016;35(3):417-428. <https://www.ncbi.nlm.nih.gov/pubmed/26751990>
5. McAnena L, Doyle F, O'Keefe M. Cross-linking in children with keratoconus: a systematic review and meta-analysis. *Acta Ophthalmol*. 2017;95(3):229-239. <https://www.ncbi.nlm.nih.gov/pubmed/27678078>
6. Kobashi H, Rong SS. Corneal Collagen Cross-Linking for Keratoconus: Systematic Review. *Biomed Res Int*. 2017;2017:8145651. <https://www.ncbi.nlm.nih.gov/pubmed/28691035>
7. Li J, Ji P, Lin X. Efficacy of corneal collagen cross-linking for treatment of keratoconus: a meta-analysis of randomized controlled trials. *PLoS One*. 2015;10(5):e0127079. <https://www.ncbi.nlm.nih.gov/pubmed/25985208>
8. Sykakis E, Karim R, Evans JR, et al. Corneal collagen cross-linking for treating keratoconus. *Cochrane Database Syst Rev*. 2015(3):CD010621. <https://www.ncbi.nlm.nih.gov/pubmed/25803325>
9. Liu Y, Liu Y, Zhang YN, et al. Systematic review and Meta-analysis comparing modified cross-linking and standard cross-linking for progressive keratoconus. *Int J Ophthalmol*. 2017;10(9):1419-1429. <https://www.ncbi.nlm.nih.gov/pubmed/28944203>
10. Li W, Wang B. Efficacy and safety of transepithelial corneal collagen crosslinking surgery versus standard corneal collagen crosslinking surgery for keratoconus: a meta-analysis of randomized controlled trials. *BMC Ophthalmol*. 2017;17(1):262. <https://www.ncbi.nlm.nih.gov/pubmed/29282020>
11. Shajari M, Kolb CM, Agha B, et al. Comparison of standard and accelerated corneal cross-linking for the treatment of keratoconus: a meta-analysis. *Acta Ophthalmol*. 2018. <https://www.ncbi.nlm.nih.gov/pubmed/29855152>
12. Wen D, Song B, Li Q, et al. Comparison of Epithelium-Off Versus Transepithelial Corneal Collagen Cross-Linking for Keratoconus: A Systematic Review and Meta-Analysis. *Cornea*. 2018;37(8):1018-1024. <https://www.ncbi.nlm.nih.gov/pubmed/29847492>

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13. Hayes. Medical Technology Directory. Comparative Effectiveness Review. Corneal Cross-Linking for Treatment of Keratoconus. Published 02/15/2018. Annual Review: Mar 15, 2019. <https://evidence.hayesinc.com/report/dir.corneal1798>. Accessed 04/23/2020.
14. Wan Q, Wang D, Ye H, Tang J, Han Y. A review and meta-analysis of corneal cross-linking for post-laser vision correction ectasia. *J Curr Ophthalmol*. 2017;29(3):145-153. <https://www.ncbi.nlm.nih.gov/pubmed/28913504>
15. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. *Journal of cataract and refractive surgery*. 2011;37(1):149-160. <https://www.ncbi.nlm.nih.gov/pubmed/21183110>
16. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *Journal of cataract and refractive surgery*. 2011;37(7):1282-1290. <https://www.ncbi.nlm.nih.gov/pubmed/21700105>
17. Greenstein SA, Shah VP, Fry KL, Hersh PS. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *Journal of cataract and refractive surgery*. 2011;37(4):691-700. <https://www.ncbi.nlm.nih.gov/pubmed/21420594>
18. Greenstein SA, Fry KL, Hersh PS. In vivo biomechanical changes after corneal collagen cross-linking for keratoconus and corneal ectasia: 1-year analysis of a randomized, controlled, clinical trial. *Cornea*. 2012;31(1):21-25. <https://www.ncbi.nlm.nih.gov/pubmed/21993470>
19. Hersh PS, Stulting RD, Muller D, Durrie DS, Rajpal RK, Group USCS. U.S. Multicenter Clinical Trial of Corneal Collagen Crosslinking for Treatment of Corneal Ectasia after Refractive Surgery. *Ophthalmology*. 2017;124(10):1475-1484. <https://www.ncbi.nlm.nih.gov/pubmed/28655538>
20. Garcia-Ferrer FJ, Akpek EK, Amescua G, et al. Corneal Ectasia Preferred Practice Pattern(R). *Ophthalmology*. 2019;126(1):P170-P215. <https://www.ncbi.nlm.nih.gov/pubmed/30366794>
21. National Institute for Health and Care Excellence (NICE). Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus and keratectasia. Interventional procedures guidance [IPG466] Published: 09/2013. <https://www.nice.org.uk/guidance/ipg466>. Accessed 04/23/2020.
22. U.S .Food & Drug Administration (FDA). Drugs@FDA: FDA-Approved Drugs. PHOTREXA® VISCOUS, PHOTREXA® and KXL™ System . NDA: 203324. Avedro, Inc. Approved: 04/14/2016. Expanded approval indications: 07/15/2016. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=203324>. Accessed 04/23/2020.