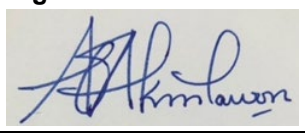
Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: AmeriHealth Caritas Pennsylvania Community HealthChoices	**Submission Date**: May 26, 2021
Policy Number: CCP.1415	**Effective Date:** 6/2019 **Revision Date:** May 4, 2021
Policy Name: Photrexa®	
Type of Submission – Check all that apply: ☑ **New Policy** ☐ **Revised Policy*** ☐ **Annual Review – No Revisions** ☐ **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:**	
Name of Authorized Individual (Please type or print): Akintayo Akinlawon, MD	**Signature of Authorized Individual:** 

Photrexa®

Clinical Policy ID: CCP.1415

Recent review date: 5/2021

Next review date: 9/2022

Policy contains: Keratoconus; collagen; refractive surgery of cornea.

AmeriHealth Caritas Pennsylvania Community HealthChoices has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania Community HealthChoices when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania Community HealthChoices will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania Community HealthChoices' clinical policies are not guarantees of payment.

Coverage policy

Photrexa®, a method of corneal cross-linking using riboflavin and ultraviolet A radiation, is clinically proven, and therefore, medically necessary for the following conditions:

- To treat progressive keratoconus or for corneal ectasia after refractive surgery.
- As a treatment after conservative interventions have failed (Andreanos, 2017; Belin, 2018; Denny, 2015).

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Routine patient evaluation and management by a network health care provider.

Background

Keratoconus is a type of corneal ectasia, along with pellucid marginal degeneration, posterior keratoconus and post-laser refractive surgery ectasia. Keratoconus is a rare ocular disease, affecting one in 2,000 Americans (Kaufman, 2016). The disease causes the cornea to experience thinning and changes in shape. The normally

round cornea develops a cone-shaped bulge at its center, in areas where thinning is greatest. It causes blurry/distorted vision, sensitivity to light, and other vision problems.

The disorder often starts at puberty and is often observed in teenagers or young adults. Males, African Americans, and Latinos are at greater risk for the disease developing. Children with the disorder have a much greater proportion of severe (stage IV) cases than do adults (27.8% versus 7.8% [Badawi, 2017]). While no cause has been identified, environmental and genetic factors are suspected (National Organization of Rare Disorders, 2016).

Pediatric keratoconus is often not diagnosed, and thus not treated. After diagnosis, compliance is often poor, even though pediatric progression is more rapid than in adult cases. Corneal transplants in children have a higher risk of rejection and poor visual progress. Intracorneal ring segment implants in children is generally safe, but not many studies exist (Olivo-Payne, 2019).

The condition is worsened by vigorously rubbing the eyes. Diagnosing the disease is feasible during a routine eye examination. Symptoms in the early stage include mild vision blurring, slightly distorted vision, sensitivity to light, and eye redness or swelling. Later stages include symptoms such as highly distorted nearsightedness and astigmatism, and inability to wear contact lenses due to the bulging cornea. Treatment of keratoconus often begins with corrective glasses or contact lenses that are rigid and gas-permeable to change the cornea back to its normal shape (Boyd, 2017).

In some cases that do not respond to glasses and contact lenses, treatment can include intracorneal ring segments (insertion of two tiny plastic pieces to reshape the cornea) or a corneal transplant (keratoplasty) (Olivo-Payne, 2019).

On April 15, 2016, the U.S. Food and Drug Administration approved Photrexa Viscous (riboflavin 5′-phosphate in 20% dextran ophthalmic solution) and Photrexa (riboflavin 5′-phosphate ophthalmic solution) and the KXL® system for corneal collagen cross-linking for patients with progressive keratoconus and corneal ectasia after refractive surgery (Food and Drug Administration, 2016). Photrexa is the first Food and Drug Administration-approved treatment for keratoconus (Kaufman, 2016).

Corneal collagen cross-linking with Photrexa is a procedure in which the epithelium is first abraded with a blunt spatula to allow penetration of riboflavin into the corneal tissue. Riboflavin eye drops are applied to the corneal surface five minutes before the procedure and every five minutes during the procedure. The corneal surface is exposed to ultraviolet A radiation, typically for about 30 minutes. Topical antibiotics and anti-inflammatory drops are usually prescribed after the procedure; in some cases, topical steroids may be necessary. One eye at a time is treated; repeat procedures may be necessary (National Institute for Health and Care Excellence, 2013).

Corneal cross-linking is a minimally invasive procedure performed in outpatient settings, lasting about 60 to 90 minutes. The procedure can prevent patients from undergoing corneal transplants, a much more invasive surgery (WebMD, 2019). The initial report on riboflavin/ultraviolet corneal cross-linking was published in 2003, and since has been widely used outside the United States for treatment of progressive keratoconus and post-laser in situ keratomileusis ectasia (Belin, 2018).

Findings

The corneal cross-linking procedure using the standard Dresden protocol is established as the gold standard for treatment of progressive keratoconus, according to an article published in October 2018 by a multinational group of experts. One of the authors is an employee of Avedro Inc. of Waltham, Massachusetts, the manufacturer of Photrexa (Belin, 2018).

A guideline for keratoconus by the American Academy of Ophthalmology acknowledged that the first surgical option for keratoconus that is non-responsive to conservative treatment is corneal cross-linking, outside the United States; the guidelines were published just before Food and Drug Administration approved Photrexa (Denny, 2015). Other keratoconus guidelines by European experts cited numerous studies that upheld the ability of corneal cross-linking to improve visual acuity and topographic indices in a safe manner for persons with keratoconus, since the technique's introduction in the late 1990s (Alio, 2015; Andreanos, 2017; National Institute for Health and Care Excellence, 2013).

One of the larger published studies of corneal cross-linking prior to the Food and Drug Administration approval of Photrexa included 152 children ages 10 to 18 years, divided into groups of corneal thickness of greater than 450 µm and less than 450 µm. Riboflavin-ultraviolet A-induced corneal cross-linking was performed on all subjects. Thirty-six months later, additional Snellen lines for uncorrected and best spectacle-corrected visual acuity were observed for the thicker group (+0.18 and +0.16) and thinner group (+0.14 and +0.15), both considered good functional improvements by authors (Caporossi, 2012).

A systematic review/meta-analysis of 17 studies assessed outcomes of three groups that 1) combined intracorneal ring segment and corneal collagen cross-linking the same day, 2) performed the ring segment at an earlier day, and 3) performed collagen crosslinking at an earlier day. After 12 months, there was no difference between the groups in best-corrected visual acuity and cylindrical refractive error (Hashemi, 2018).

A systematic review/meta-analysis of 24 studies compared standard collagen cross-linking with cross-linking modified to reduce complications. The modified group was significantly inferior at delaying Kmax deterioration ($P = .03$). The spherical equivalent decreased significantly for the standard group ($P < .00001$) (Liu, 2017).

A meta-analysis of seven studies (n = 283) eyes compared accelerated corneal collagen cross-linking with conventional corneal collagen cross-linking to treat keratoconus. Greater reductions of average keratometry were found in the accelerated group ($P < .01$), while other outcomes were not significantly different between the two groups (Jiang, 2019).

Another comparison of outcomes after accelerated versus conventional cross-linking was a meta-analysis of 22 studies (n = 1,158) eyes. The most recent follow-up revealed conventional cross-linking yielded better results for minimum keratometry ($P < .00001$) and demarcation line depth ($P < .00001$). Accelerated cross-linking had superior results when minimum corneal thickness was considered ($P = .0005$). Other measures showed no significant differences between the two groups (Shajari, 2019).

A meta-analysis (11 studies) of outcomes after epithelial off-standard cross-linking with accelerated versus conventional cross-linking for keratoconus yielded mixed results. Epithelial procedures had a greater reduction in maximum keratometry, while accelerated procedures had superior results in central corneal thickness and endothelial cell density (Wen, 2018).

A meta-analysis of three randomized controlled trials (n = 244 eyes) found those who underwent standard corneal collagen crosslinking on keratoconus had more effective reduction in maximum keratometry at least 12 months post-operative. Significantly greater corrected distant visual acuity was observed in those who underwent transepithelial corneal collagen crosslinking, with similar results between groups in uncorrected distant visual acuity. Safety was similar for both groups (Li, 2017). A systematic review/meta-analysis of 12 studies (n = 966) found the transepithelial approach to crosslinking inferior to the epithelium-off corneal approach, measured in maximal keratometry at 12 months (P = .004) and longest follow-up (P < .001) (Nath, 2020).

A systematic review of collagen cross-linking for keratoconus consisted of five randomized controlled trials (n = 289 eyes). Compared to no treatment, after one year, cross-linking was significantly more effective in best spectacle correction of visual acuity. No significant changes in corneal thickness and cylindrical refraction were observed. Authors cite heterogeneity and paucity of randomized trials as limits to drawing conclusions on efficacy (Kobashi, 2017).

A systematic review/meta-analysis of corneal collagen cross-linking among children (average age = 15 years) included 13 studies (n = 490 eyes). The review documented significant improvement in uncorrected and best-corrected visual acuity after 12 months, and stable results after 24 months, along with improved maximum keratometry for the standard protocol group. All three measures were stable at 12 months in the trans-epithelial group. Authors caution that more and longer-term studies are needed to confirm these results (McAnena, 2017).

A systematic review/meta-analysis of corneal collagen cross-linking found improved visual acuity of 1 to 2 Snellen lines three months or more after the procedure; improved topography parameters (0.6 – 1 diopter) after 12 to 24 months; improved refractive cylinder by 0.4 to 0.7 diopters; improved (decreased) endothelial cell density by 225 cells/mm^2 after three months but then returned to normal; and reduced corneal thickness by 10 to 20 µm after one year but not after 24 months (Meiri, 2016).

A systematic review of 17 studies of pediatric patients with keratoconus concluded that epithelium-off cross-linking (removing the epithelium before putting in the drops) is safe and effective to prevent keratoconus progression in pediatric patients, despite progression being identified in 22% of the treated eyes (Godefrooij, 2016a). Epi-on involves loosening of the epithelium with eye drops or a sponge before putting in the eye drops.

A systematic review/meta-analysis of 95 studies (n = 4,560) showed treatment of keratoconus with a combination of intracorneal ring segment implantation, collagen cross-linking, and photorefractive keratectomy is superior to the implantation alone in all measures except for the correction of spherical equivalent, and could be proposed to young people with keratoconus (Benoist d'Azy, 2019).

A study of 400 eyes in 301 patients, each of whom underwent corneal collagen cross-linking for keratoconus, analyzed results by age group (<18, 18-29, 30-39, and >40 years). Results, in terms of best-corrected visual acuity, regularization of corneal shape, and reduction of coma, found that all groups had positive results, most superior for subjects age 18-29 and 30-39 (Vinciguerra, 2013).

In a study comparing the number of corneal transplants in the Netherlands before (2005 - 2007) and after (2012 - 2014) the country's introduction of corneal cross-linking, a significant decline from 269 to 201 (P < .005) was observed (Godefrooji, 2016b).

References

On February 8, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were keratoconus; collagen; refractive surgery of cornea. We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

Policy updates

4/2019: initial review date and clinical policy effective date: 6/2019

5/2020. Policy references updated.

5/2021: Policy references updated.