



Medical Policy Manual

Draft Revised Policy: Do Not Implement

Corneal Collagen Cross-Linking

DESCRIPTION

Corneal collagen cross-linking (CXL) is a photochemical procedure used in the treatment of progressive keratoconus and corneal ectasia. Keratoconus is a naturally occurring dystrophy of the cornea characterized by progressive deformation (steepening) of the cornea while corneal ectasia is keratoconus that occurs after refractive surgery. Both lead to functional loss of vision and need for corneal transplantation. The goal of keratoconus treatment is to reshape the abnormal cornea into a normal dome-like shape, which allows light entering the eye to focus on the retina, improving current visual function and preventing additional vision loss.

CXL is performed with the photosensitizer riboflavin (vitamin B2) and ultraviolet-A (UVA) irradiation. Using the epithelium-off (also known as epi-off) 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 with UVA at a maximal wavelength to allow for absorption by 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.

Epithelium-on, also known as epi-on or transepithelial, is another method of corneal collagen cross-linking. In this method, the corneal epithelial surface is left intact or is partially disrupted and a longer riboflavin loading time is required.

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POLICY

- Corneal collagen cross-linking may be considered **medically necessary** if the medical appropriateness criteria are met. **(See Medical Appropriateness below.)**
- Corneal collagen cross-linking for the treatment of other conditions/diseases, ~~including use of the epithelium-on (epi-on or transepithelial) method,~~ is considered **investigational**.

MEDICAL APPROPRIATENESS

- Corneal collagen cross-linking is considered **medically appropriate** if **ALL** the following are met:
 - Treatment is indicated for **ANY ONE** of the following conditions:
 - Progressive keratoconus
 - Corneal ectasia after refractive surgery
 - Failure of conservative treatment (e.g., spectacle correction, rigid contact lens)
 - Treatment with **ANY ONE** of the following:
 - Photrexa®
 - Epioxa™ for individuals age 13 years or older

IMPORTANT REMINDERS

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- Any specific products referenced in this policy are just examples and are intended for illustrative purposes only. It is not intended to be a recommendation of one product over another and is not intended to represent a complete listing of all products available. These examples are contained in the parenthetical e.g. statement.
- We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the medical policy and a health plan or government program (e.g., TennCare), the express terms of the health plan or government program will govern.

ADDITIONAL INFORMATION

In 2016, riboflavin 5'-phosphate in 20% dextran ophthalmic solution (Photrexa Viscous®; Avedro) and riboflavin 5'-phosphate ophthalmic solution (Photrexa®; Avedro) were approved by the U.S. Food and Drug Administration (FDA) for use with KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia after refractive surgery. Photrexa products are expected to be withdrawn from the market effective January 20, 2026 with manufacturing ending in February 2026.

In 2025, the FDA approved riboflavin 5'-phosphate 0.177% and 0.239% ophthalmic solution (Epioxa™ and Epioxa HD™; Glaukos) for treatment of keratoconus in adults and children aged 13 years and older. Epioxa uses the O2n System™ and Boost Googles® for its proprietary epithelium-on corneal collagen cross-linking technology.

SOURCES

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EFFECTIVE DATE

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