

Utilization Management and Clinical Medical Policy

Policy Name: Epioxa and Epioxa HD (riboflavin 5'-phosphate ophthalmic solution)	Policy Number: MP-RX-FP-186-26	Scope: <input checked="" type="checkbox"/> MMM MA <input checked="" type="checkbox"/> MMM MultiHealth	Origination Date: 5/6/2026	Effective Date: 5/6/2026
			Last Review Date: 5/6/2026	Frequently Revision: Annual

Service Category:

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|--|---|
| <input type="checkbox"/> Anesthesia | <input type="checkbox"/> Medicine Services and Procedures |
| <input type="checkbox"/> Surgery | <input type="checkbox"/> Evaluation and Management Services |
| <input type="checkbox"/> Radiology Procedures | <input type="checkbox"/> DME/Prosthetics or Supplies |
| <input type="checkbox"/> Pathology and Laboratory Procedures | <input checked="" type="checkbox"/> Other: Part B Drugs |

Service Description:

This document addresses the use of Epioxa HD and Epioxa, riboflavin 5'-phosphate ophthalmic solutions approved by the U.S. Food and Drug Administration (FDA) for use in epithelium-on corneal collagen cross-linking (CXL) for the treatment of keratoconus in adults and pediatric patients aged 13 years and older. Epioxa HD and Epioxa are topical ophthalmic photoenhancers administered sequentially during a corneal cross-linking procedure in conjunction with ultraviolet-A (UV-A) irradiation and supplemental oxygen. The therapy is designed to strengthen corneal collagen fibers and stabilize progressive corneal steepening without requiring removal of the corneal epithelium.

Background Information:

Keratoconus is a progressive corneal ectatic disorder that can result in irregular astigmatism and visual impairment. Spectacles and specialty contact lenses may improve vision but do not alter disease progression. Corneal collagen cross-linking (CXL) is intended to stabilize the cornea by strengthening stromal collagen fibers using riboflavin and ultraviolet-A (UV-A) light.

The objective of cross-linking is to slow or halt progression rather than to correct refractive error. Traditional "epithelium-off" CXL requires mechanical removal of the corneal epithelium to facilitate riboflavin penetration. Clinical studies have demonstrated that CXL reduces progression, induces corneal flattening, and stabilizes or improves visual acuity, with durability reported in long-term follow-up studies extending up to 10 years. However, epithelial removal is associated with postoperative pain, delayed epithelial healing, risk of infection, corneal haze, and temporary visual disturbance. CXL is generally indicated for documented progressive keratoconus and is not recommended for stable disease. It is typically avoided in patients with active or prior herpetic keratitis, markedly thin corneas, or acute corneal hydrops.

In October 2025, the U.S. Food and Drug Administration approved Epioxa HD and Epioxa for use in epithelium-on corneal collagen cross-linking in adults and pediatric patients aged 13 years and older with keratoconus. Epioxa HD and Epioxa are not alternative therapies but complementary components of a single, FDA-approved treatment protocol. The two formulations are administered sequentially during the same procedural session, with Epioxa HD applied first followed by Epioxa prior to ultraviolet-A irradiation. Both products are required to complete the epithelium-on corneal collagen

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cross-linking procedure and are not intended for standalone use. Accordingly, they represent components of one integrated therapeutic procedure rather than separate treatment options. Unlike epithelium-off CXL, this procedure does not require epithelial removal.

Approval was supported by two Phase 3, randomized, parallel-group, sham-controlled trials (NCT03442751 and NCT05759559). In both studies, eyes were randomized 2:1 to CXL or sham treatment and followed for 12 months. The primary efficacy endpoint was change from baseline in maximum corneal curvature (Kmax).

In Study 1 (279 treated eyes), a statistically significant treatment effect was demonstrated at Month 6, with a -1.0 diopter (D) difference in Kmax change between CXL and sham ($p < 0.01$), which was sustained at Month 12 (-1.1 D; $p < 0.01$). In Study 2 (312 treated eyes), a statistically significant treatment effect was observed at Month 12 (-1.0 D; $p < 0.01$), with supportive findings at Month 6 (-0.6 D; $p < 0.01$). Subgroup analyses demonstrated greater treatment effects in younger patients, reflecting stabilization or improvement in treated eyes and continued steepening in sham-treated eyes.

The most commonly reported adverse reaction was conjunctival hyperemia (31%). Other adverse reactions occurring in 5% to 25% of treated eyes included corneal opacity (haze), photophobia, punctate keratitis, eye pain, eye irritation, increased lacrimation, corneal epithelium defect, eyelid edema, corneal striae, reduced visual acuity, dry eye, and anterior chamber flare.

Across both trials, epithelium-on CXL demonstrated statistically significant reduction in corneal steepening compared with sham control through 12 months of follow-up, with a safety profile characterized primarily by ocular surface and transient inflammatory findings.

Approved Indications

- A. Epioxa HD and Epioxa are indicated for use in epithelium-on corneal collagen cross-linking for the treatment of keratoconus in adults and pediatric patients aged 13 years and older, in conjunction with the O2n System and the Boost Goggles.

Other Uses

- A. See background section above.

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Medical Necessity Guidelines:

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Epioxa and Epioxa HD® (riboflavin 5'-phosphate ophthalmic solutions)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.*)

- i. Member has a diagnosis of keratoconus; **AND**
- ii. Member is 13 years of age or older; **AND**
- iii. Documentation of progressive keratoconus in the eye to be treated within the previous 12–24 months, defined as:
 - A. An increase in maximum keratometry (Kmax) of ≥ 1.0 diopter (D); **OR**
 - B. Other objective corneal topographic or tomographic evidence of progression consistent with keratoconus (e.g., documented increase in corneal steepening or thinning) as determined by the treating ophthalmologist; **AND**
- iv. The procedure will be performed in conjunction with the FDA-required UV-A irradiation system and supplemental oxygen delivery system (O2n System and Boost Goggles); **AND**
- v. The member does not have advanced corneal scarring that would preclude meaningful benefit from cross-linking.

B. Criteria For Continuation of Therapy

- i. Repeat treatment of the same eye with Epioxa HD and Epioxa is not routinely authorized, as corneal collagen cross-linking is generally considered a one-time per eye procedure.
- ii. MMM considers repeat treatment medically necessary in members requesting reauthorization for an indication listed in Section I above (Initial Authorization Criteria) when there is documentation of continued keratoconus progression after prior

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cross-linking and no evidence of unacceptable adverse effects attributable to the initial procedure. Retreatment must be consistent with FDA labeling and device instructions for use.

- iii. The following information must be submitted for reauthorization:
 - A. A current ophthalmology note documenting the member’s clinical course following prior cross-linking, including assessment of treatment response and clinical rationale for repeat treatment.
 - B. Current corneal topography or tomography demonstrating objective evidence of continued progression (e.g., increase in maximum keratometry [Kmax] or other corneal steepening parameters) when compared with prior measurements.

C. Authorization Duration

- i. Initial Approval Duration: 6 months
- ii. Reauthorization Approval Duration: 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

- i. Requests for Epioxa HD and Epioxa when the above criteria (Section I: Initial Authorization Criteria) are not met.
- ii. Use for indications other than epithelium-on corneal collagen cross-linking for the treatment of keratoconus in adults and pediatric patients aged 13 years and older.
- iii. Use for stable keratoconus without documented progression.

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Limits or Restrictions:

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

- i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Approved Indication	Recommended Dosing/Limits
Keratoconus	<ul style="list-style-type: none"> Epioxa HD is supplied as a 0.239% (2.39 mg/mL) riboflavin 5'-phosphate ophthalmic solution in a single-dose glass syringe. Epioxa is supplied as a 0.177% (1.77 mg/mL) riboflavin 5'-phosphate ophthalmic solution in a single-dose glass syringe. Coverage is limited to one treatment episode per eye. Each treatment episode consists of the FDA-approved sequential administration of Epioxa HD followed by Epioxa during a single procedure.
Exceptions	
None	

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Codes Information:

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

ICD-10 Diagnostic Codes:

Codes	Description
H18.601	Keratoconus, unspecified, right eye
H18.602	Keratoconus, unspecified, left eye
H18.603	Keratoconus, unspecified, bilateral
H18.611	Keratoconus, stable, right eye
H18.612	Keratoconus, stable, left eye
H18.613	Keratoconus, stable, bilateral
H18.621	Keratoconus, unstable, right eye
H18.622	Keratoconus, unstable, left eye
H18.623	Keratoconus, unstable, bilateral

HCPCS Codes:

Codes	Description
J2787	Riboflavin 5'-phosphate, ophthalmic solution, up to 3 ml

CPT Codes:

Codes	Description
0402T	Collagen cross-linking of cornea, including removal of the corneal epithelium, when performed, and intraoperative pachymetry, when performed

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Reference Information:

1. Epioxa HD and Epioxa [prescribing information]. Aliso Viejo, CA: Glaukos Corporation; October 2025.
2. Glaukos Corporation. Epioxa™ Billing and Coding Guide: A Step-by-Step Guide to Billing and Coding. PM-US-3251-V-1. February 2026. Available at: <https://www.epioxa.com/wp-content/uploads/2026/02/PM-US-3251-V-1-Epioxa-Billing-and-Coding-Guide.pdf>. Accessed February 23, 2026.
3. Glaukos Corporation. Glaukos Announces FDA Approval of Epioxa™. October 20, 2025. Available at: <https://investors.glaukos.com/news/news-details/2025/Glaukos-Announces-FDA-Approval-of-Epioxa/default.aspx>. Accessed February 23, 2026.
4. Maskill D, Okonkwo A, Onsiong C, et al. Repeat corneal collagen cross-linking after failure of primary cross-linking in keratoconus. *British Journal of Ophthalmology* 2024;108:662-666.
5. Wayman LL, Jacobs DS, Li H. Keratoconus. In: UpToDate. Waltham, MA: UpToDate Inc. Literature review current through January 2026. Topic last updated May 31, 2024. Accessed February 23, 2026.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy History:

Type of Review	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Policy Inception	New policy creation.	3/9/2026	5/6/2026