INDICATIONS FOR USE
# Table of Contents

**PROKERA® Indications Overview** .......................................................... 1

## Ocular Surface Disease

No need for epithelial debridement:

- Neurotrophic PED ................................................................. 3
- Infectious Keratitis ............................................................. 5
- Filamentary Keratitis ............................................................ 7
- Dry Eye Syndrome, Exposure Keratopathy .................................. 9

Needs epithelial debridement:

- Recurrent Corneal Erosion .................................................... 11
- Salzmann's Nodular Degeneration .......................................... 13
- Post-DSEK for Bullous Keratopathy ....................................... 15

## Refractive: Before & After Corneal/Cataract Refractive Surgeries

- Post-PRK Haze ........................................................................ 17

## Physician Biographies & References .................................................. 19
**PROKERA® Indications Overview**

**Ocular Surface Indications**

**Diseases with Pre-existing Epithelial Defects**
- to promote wound healing and reduce complications (debridement is optional)
  - Neurotrophic Persistent Corneal Epithelial Defect
  - Post-Infectious Recalcitrant Corneal Ulcers (e.g., herpetic, vernal, and bacterial)
  - Non-Healing Epithelial Defect After PRK/PTK
  - Acute Chemical/Thermal Burns
  - Acute Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

**Diseases without Epithelial Defects**
- to prevent further damage and promote regeneration (no debridement/PTK)
  - Dry Eye Syndrome
  - Superficial (Punctate) Keratitis
  - Filamentary Keratitis
  - Radiation Keratitis; whorl pattern indicative of limbal stem cell injury
  - Exposure (Graves) Keratopathy

**Diseases with Unhealthy Epithelium or Basement Membrane**
- to promote regeneration (after debridement/PTK)
  - Recurrent Corneal Erosion
  - Salzmann’s Nodular Degeneration
  - Bullous Keratopathy during/following DSEK
  - Haze after PTK
  - Partial Limbal Stem Cell Deficiency
  - Corneal Dystrophy (e.g., Reiss Buckler)

**Refractive Indications**

**Before Surgery**
- To treat pre-existing ocular surface disorders and restore corneal integrity before refractive, cornea, or cataract surgery

**After Surgery**
- To promote wound healing
  - To prevent post-PRK haze

PROKERA® is a 16mm device that conforms to the ocular surface.
**Neurotrophic Persistent Corneal Epithelial Defect**

**Overview**

Neurotrophic persistent corneal epithelial defect (PED) is a degenerative corneal disease induced by an impairment of the trigeminal nerve. Impairment or loss of corneal sensory innervation is responsible for corneal epithelial defects, ulcer, and perforation. Neurotrophic PED is also characterized by decreased corneal sensation, epithelial breakdown, and poor healing. Coexisting ocular surface diseases such as dry eye, exposure keratitis, and limbal stem cell deficiency may worsen the prognosis. The disease progression is often asymptomatic and may lead to corneal infection and melting/perforation. Conventional treatments fail to promote prompt healing and tend to leave a corneal scar if healing does not occur immediately. Cryopreserved amniotic membrane contains nerve growth factor (NGF), which facilitates epithelial healing and helps recover corneal sensitivity.

**Diagnosis**

- **History:** Previous herpes simplex virus (HSV) keratitis, diabetes, surgery, or irradiation
- **Symptoms:** Blurry vision with minimal discomfort
- **Examination:** Central or paracentral epithelial defect (with fluorescein staining), infrequent blinking, decreased corneal sensation, and low tear meniscus
- **Microbiological examination should be performed to exclude bacterial, fungal, or viral infections if there is inflammatory infiltrate**

**Treatment Strategy**

- Restore corneal integrity by reducing inflammation, promoting healing, and preventing haze (PROKERA®) together with tapesorrhaphy
- Treat underlying cause (eg, antiviral)
- Treat associated dry eye (punctal occlusion)
- Prevent further damage (withdraw unnecessary topical drugs)
- Reduce the risk of secondary infections (avoid bandage contact lens [BCL])

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**Case Study**

- A 67-year-old patient had a history of HSV keratitis and dry eye. She presented with mild ocular discomfort and progressive diminution of vision (20/400) over several weeks
- Examination revealed a central corneal epithelial defect surrounded by a rim of loose epithelium, stromal edema, and anterior chamber inflammatory reaction (Fig. A, C)
- PROKERA® was placed along with punctal plug, tapesorrhaphy, and oral Acyclovir
- Complete healing occurred within one week, resulting in clear cornea, 20/20 vision, and improved tear meniscus (Fig. B, D)

**Conclusion**

Early intervention with placement of PROKERA® promotes regenerative healing and prevents haze.
**Infectious Keratitis**

**Overview**

Infectious keratitis is a serious sight-threatening ocular infection and one of the most significant complications of contact lens usage. Damage to the cornea can occur rapidly and early diagnosis and treatment are essential. The principal therapeutic goal is to eliminate the pathogens and to prevent irreversible corneal structural damage. After the pathogen is identified by microbiological workup, topical antimicrobial therapies take precedence to sterilize the corneal lesion. Despite the control of infection, corneal melting/damage/scarring may occur due to digestive enzymes released by inflammatory and immune reactions to microbes. Cryopreserved amniotic membrane is well known to have potent anti-inflammatory and anti-scarring properties that promote healing and prevent corneal melt and scar formation. In addition, due to its therapeutic effects, cryopreserved amniotic membrane may also facilitate reduced steroid usage.

**Diagnosis**

- **History:** Injury, contact lens usage, or surgery
- **Symptoms:** Pain, photophobia, lacrimation, and loss of vision
- **Examination:** Corneal epithelial defect with infiltrate or ulcer, corneal edema, and hypopyon

**Treatment Strategy**

- Perform scraping and microbial culture
- Treat infection with fortified broad-spectrum antibiotics, which will be modified according to culture results
- Treat the inflammation and prevent corneal melting (PROKERA®)
- Restore corneal integrity by promoting healing and reducing haze (PROKERA®)

**Case Study**

- A 61-year-old LASIK and contact lens wearer presented with severe ocular pain and loss of vision
- Examination revealed a central corneal ulcer, deep stromal infiltrate, hypopyon, and severe conjunctival inflammation (Fig. A, C)
- Corneal scraping and culture were followed by fortified antibiotics. Microbiologic workup confirmed the diagnosis of staphylococcus aureus
- PROKERA® was placed and fortified antibiotics were tapered to QID
- Two weeks later, inflammation was markedly reduced, the corneal epithelial defect completely healed, and the patient regained 20/25 vision (Fig. B, D)

**Conclusion**

Early intervention by PROKERA® promotes epithelialization, and reduces pain, inflammation, and haze in severe bacterial keratitis.
**Filamentary Keratitis**

**Overview**
Filamentary keratitis is a chronic corneal condition characterized by multiple filaments attached to areas of compromised corneal epithelium. The filaments can be quite extensive and may enmesh calcareous granules, bacteria, and dust particles. Blinking lids pull on the loose ends of the filaments, stimulating the pain-sensitive corneal nerves and creating multiple epithelial defects. Patients often experience foreign body sensation, discomfort, photophobia, pain, and blurry vision. Filamentary keratitis most often accompanies dry eye syndrome and patients may also have underlying systemic conditions, particularly connective tissue disorders. Cryopreserved amniotic membrane contains anti-inflammatory mediators and complex arrays of growth factors and cytokines, which help regenerate a healthy corneal epithelium and may reduce the recurrence.

**Diagnosis**
- Symptoms: Ocular discomfort, foreign body sensation, pain, photophobia, and blurred vision.
- Examination:
  - Tadpole-shaped mucus filaments adhering to the corneal surface, with the tails floating freely within the tear film
  - Rose bengal dye makes the filaments more readily visible on biomicroscopy
  - Reduced tear break-up time and punctate epithelial keratopathy

**Treatment Strategy**
- Treat ocular surface inflammation (non-preserved steroids)
- Treat associated dry eye (Artificial tears/Punctal occlusion)
- Restore corneal integrity (PROKERA®)
- Prophylactic antibiotics if necessary

**Case Study**
- A 68 year-old female presented with acute ocular pain, photophobia, and blurred vision (20/70) for 3 days. She had a history of similar repeated attacks as well as dry eye (treated with artificial tears and punctal plugs)
- Diagnosis of filamentary keratitis was confirmed based on the clinical findings of positively stained mucus strands attached to the cornea (Fig. A, C)
- Numerous treatment regimens were implemented, including non-preserved artificial tears, lubricating ointment, and topical steroids for two months without success
- Without debridement, PROKERA® was placed for 3 days. Her symptoms were completely relieved, filaments disappeared, and the cornea became clear (Fig. B, D). Her vision improved to 20/40

**Conclusion**
Filamentary keratitis is a recurrent and incapacitating condition that may prove difficult to manage. PROKERA® effectively treated the above patient and restored a healthy corneal epithelium.
Dry Eye Syndrome, Exposure Keratopathy

Overview
Dry eye syndrome (DES) is characterized by tear film instability and ocular surface inflammation, which in turn causes cell damage, resulting in a self-perpetuating cycle of deterioration. Several pro-inflammatory cytokines including Interleukin 1 (IL-1), IL-6, IL-8, transforming growth factor beta (TGF-ß), and tumor necrosis factor (TNF-α) are up-regulated in DES. Elevated levels of tissue-degrading enzymes such as matrix metalloproteinases (MMPs) are also noted. DES may be complicated by sterile or infectious corneal ulceration, corneal perforation, and blindness. Cryopreserved amniotic membrane contains anti-inflammatory mediators, a myriad of growth factors and cytokines, and a regenerative matrix that are important to help restore a healthy and non-inflamed ocular surface and maintain a stable tear film.

Diagnosis
- Symptoms: Ocular irritation, burning, itching, pain, foreign-body sensation, photophobia, and blurred vision
- Examination: Conjunctival injection/inflammation, decreased tear meniscus, decreased tear break-up time, increased debris in the tear film/mucous discharge, corneal filaments, irregular corneal surface, superficial punctate keratitis (SPK) with positive fluorescein staining, and corneal ulcers/infectious keratitis in severe cases

Treatment Strategy
- Administer artificial tears preferably nonpreserved
- Treat ocular surface inflammation by steroid or Restasis®
- Perform punctal occlusion with plug or cautery
- Restore corneal integrity by suppressing inflammation and restoring a healthy, normal epithelium (PROKERA®)

Case Study
- A 49-year-old female presented with persistent ocular discomfort, gritty sensation, and blurred vision (20/100) for 1 week. She had a long history of dry eye and rheumatoid arthritis, and has been treated with artificial tears, serum eye drops, punctal plugs, and scleral lens without success
- Examination showed an irregular corneal epithelium with SPK (Fig. A)
- PROKERA® was placed (Fig. C) to restore a smooth epithelium within 48 hours, resulting in complete symptomatic relief, clear cornea, and 20/20 vision (Fig. B, D)

Conclusion
PROKERA® can be used as a temporary biological bandage for severe DES to restore a healthy and smooth corneal epithelium and reduce inflammation that is crucial in maintaining a stable tear film.
Recurrent Corneal Erosion

Overview
Recurrent corneal erosion (RCE) is a common ocular disorder characterized by a disturbance at the level of the corneal epithelial basement membrane (BM), resulting in defective adhesions and recurrent breakdown of the epithelium.5 RCE may occur spontaneously or secondary to corneal injury. Predisposing factors include diabetes or corneal dystrophy.6 Patients with RCE often show increased levels of enzymes such as matrix metalloproteinases (MMPs) that dissolve the BM and its anchoring components including integrins, laminin, and type VII collagen.7

Non-cryopreserved treatments include lubricating agents, patching, bandage contact lens (BCLs), debridement, anterior stroma puncture, and phototherapeutic keratectomy (PTK). However these treatments still have a high recurrence rate and carry the risk of developing haze.6 Cryopreserved amniotic membrane contains inhibitors of MMPs and active matrix components including collagen type VII and laminin; essential for regenerative healing and prevention of recurrence.8

Diagnosis
• History: Previous corneal injury, corneal dystrophy, or diabetes
• Symptoms: Acute ocular pain, foreign-body sensation, photophobia, and tearing (upon awakening)
• Examination: Punctate epithelial erosions in milder cases (microform erosions) and a large epithelial defect or area of edematous non-adherent epithelium in severe cases (macroform erosion)

Treatment Strategy
• Relieve acute symptoms eg, pain
• Restore corneal integrity, regain epithelial attachments, and prevent recurrence (PROKERA®)
• Treat underlying cause
• Reduce the risk of secondary infections (avoid extended BCL usage)9

Case Study
• A 52-year-old female presented with ocular pain and blurred vision (20/200) for 2 weeks
• She had a history of similar attacks diagnosed as RCE. Epithelial debridement, lubricants, and BCLs failed to relieve pain and halt recurrence
• Epithelial debridement to remove loose epithelium (Fig. A, C) followed by placement of PROKERA® (Fig. B)
• On the second day, the patient had no pain
• Complete healing occurred within 3 days, resulting in clear cornea, and 20/20 vision (Fig. D)
• Cornea remained stable with no recurrence for more than 2 years follow up

Conclusion
PROKERA® rapidly resolved RCE and prevented further recurrence in this case, which failed to respond to conventional therapies.
Salzmann’s Nodular Degeneration

Overview
Salzmann’s nodular degeneration (SND) is characterized by multiple superficial blue-white nodules in the mid-periphery of the cornea. The pathogenesis is unknown and usually develops following ocular surface inflammation or surgery as an end stage of corneal scarring pathway. SND is usually asymptomatic but may affect vision if located centrally. Histologically, SND is composed of dense irregularly arranged collagen tissue between epithelium and Bowman’s layer or beyond; therefore, patients may develop recurrent corneal erosions or corneal scarring.

Surgical removal, phototherapeutic keratectomy (PTK) with or without the use of topical mitomycin-C (MMC), lamellar, or penetrating keratoplasty have been used in the treatment of this disease. Although PTK may restore a smooth ocular surface, the required laser ablation depth is significantly large and may be complicated with haze and refractive error. In contrast, superficial keratectomy followed by placement of PROKERA® is effective in restoring corneal surface integrity without haze.

Diagnosis
• History: Previous inflammation, corneal surgery
• Symptoms: Decreased vision if located centrally
• Examination: Superficial, elevated multiple bluish-white nodules located at corneal mid-periphery

Treatment Strategy
• Removal of corneal lesion (superficial keratectomy)
• Restoring corneal surface integrity by promoting healing and preventing haze (PROKERA®)

Case Study
• A 38-year-old male presented with progressive distortion of vision in both eyes 20 years after radial keratectomy
• Examination SND encroaches on the visual axis resulting in 20/70 (Fig. A)
• Superficial keratectomy was performed (Fig. C), followed by topical MMC for 25 seconds and placement of PROKERA®
• Complete epithelialization was achieved without haze in 6 days (Fig. B)
• The cornea was clear 3 weeks later and vision improved to 20/20 (Fig. D). No recurrence was noted during a 2 year follow up

Conclusion
PROKERA® allows regenerative healing to restore corneal surface integrity and improve the quality of vision after superficial keratectomy to remove Salzmann’s nodular degeneration or other similar diseases.
Post-DSEK for Bullous Keratopathy

Overview

Descemet’s stripping endothelial keratoplasty (DSEK) is currently the treatment of choice over penetrating keratoplasty in cases with bullous keratopathy due to corneal endothelial dysfunction. Advantages include faster recovery and fewer complications. In cases with pseudophakic bullous keratopathy (PBK), the stromal and epithelial edema usually interferes with intraoperative visualization and poses a major technical challenge for DSEK. Debridement of the epithelial blisters may improve the visualization during surgery; however, it creates a large, slow-healing epithelial defect.12

Cryopreserved amniotic membrane has been used successfully to treat nonhealing epithelial defects. Early intervention with cryopreserved amniotic membrane via PROKERA® enhances faster healing of a large corneal epithelial defect after DSEK in a case of PBK.

Diagnosis

- Symptoms: Ocular pain, foreign-body sensation, photophobia, and loss of vision
- Examination: Corneal opacity, edema, vascularization, and epithelial bullae/defects

Treatment Strategy

- DSEK to replace diseased endothelium
- Debridement/superficial keratectomy to remove diseased epithelium and improve visualization during DSEK
- PROKERA® placement to enhance epithelialization and reduce haze

Case Study

- An 85-year-old patient presented with light perception vision and persistent pain in the right eye following cataract surgery
- Examination revealed PBK with large corneal epithelial bullae, corneal haze, vascularization, and edema (Fig. A)
- Superficial keratectomy was performed to remove the corneal pannus and to improve visualization. DSEK was then performed through a temporal 4mm scleral tunnel. PROKERA® was placed to enhance epithelialization
- The corneal epithelium completely healed in 1 week. The superficial and deep corneal neovascularization regressed and completely vanished after 1 month. The posterior lamellar graft remained stable, and vision improved to 20/70 at 2 months, 20/50 at 2 years and 20/40 at 3 years (Fig. B)

Conclusion

PROKERA® can be used as a temporary biological bandage to restore a healthy corneal epithelium after DSEK is used to restore a functioning corneal endothelium.
Post-PRK Haze

Overview
Although the outcomes of PRK and LASIK are quite comparable at the six-month post-operative visit, PRK carries a greater risk of scarring (haze) and unpredictable healing of the cornea. Other drawbacks include significant postoperative pain, slow epithelialization and unstable vision. Usually it takes a week to recover an intact epithelium and several weeks before the best-corrected acuity is achieved after PRK. The use of steroids to modulate the healing process is controversial as it may further delay epithelialization, thus increasing the risk of developing haze. If significant corneal haze persists, phototherapeutic keratectomy (PTK) is usually applied with or without Mitomycin C along with a second course of topical steroids. Repeated PTK may fail to restore corneal transparency and in some cases may induce further haze. Cryopreserved amniotic membrane has been used to treat corneal haze induced by PRK and PTK. PROKERA® is effective not only in promoting rapid epithelialization but also in reducing inflammation and haze.13

Case Study

A 22-year-old woman had uneventful bilateral PRK for myopia. 3 months later, she complained of decreased vision in the left eye (20/100). Examination revealed dense fibrotic sub-epithelial opacities, and corneal topography showed central irregularities.

- Phototherapeutic keratectomy (PTK) was performed on a 7.0mm zone at a depth of 40µm. 3 months after retreatment, vision decreased (20/200) and corneal opacity recurred due to fibrotic sub-epithelial and anterior stromal opacities (Fig. A, C).
- PTK was repeated on a 7.0mm zone at a depth of 50µm, and PROKERA® was inserted. 3 days later complete epithelialization occurred. PROKERA® was removed and topical antibiotic steroids were tapered.
- One month later, patient restored a crystal clear cornea (Fig. B, D) and 20/20 vision. Corneal topography showed regular corneal surface which remained stable 2 years later.

Conclusion
PROKERA® can be used at an early stage of the corneal wound healing to prevent haze after PRK. It can also be used in conjunction with PTK to treat post-PRK haze. PROKERA® is effective in blocking corneal fibrosis if it could be applied immediately after PTK.

Diagnosis
- Symptoms: Reduced visual function
- Examination: Corneal opacity (sub-epithelial or anterior stromal haze)

Treatment Strategy
- Prevention of haze by early modulation of wound healing after PRK (PROKERA®)
- Debridement/Superficial keratectomy/PTK to remove scar tissue
- PROKERA® placement to reduce pain after ablation, enhance epithelialization and reduce haze
Physician Biographies

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Robert Mack, MD, is a magna cum laude graduate of Cornell University, and graduated with distinction from Case Western Reserve University School of Medicine, where he served as president of the Medical honor society. Dr. Mack is the recipient of both the Arthur J. Maschie Award for Excellence in the Art and Science of Medicine and the Irwin H. Lepow Award for Excellence in Research. He is a board-certified ophthalmologist with complete fellowship training in corneal and refractive surgery. Dr. Mack has served as an Assistant Professor of Ophthalmology at Rush Medical College and as co-investigator on several excimer laser clinical trials. He is also a member of the editorial board of the Journal of Refractive Surgery. He is not a consultant for Bio-Tissue.

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Shachar Tauber, MD, completed his medical degree and residency program at the Tulane School of Medicine in 1992. He completed several fellowships in cornea and refractive surgery. He joined the Mercy Family in 2004 after having served as Assistant Professor at Yale University Department of Ophthalmology and Visual Science as the Director of Cornea and Refractive Surgery at the Yale University School of Medicine in New Haven, Connecticut. He is respected for his work within technological advances in the LASIK field.

References
