BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

OXERVATE™ (cenegermin-bkbj) ophthalmic topical solution Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for: OXERVATE (cenegermin-bkbj)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in the diagnosis or in consultation with an Ophthalmologist or Optometrist

Indication
- Diagnosis of Stage 2 or Stage 3 neurotrophic keratitis

ORIGINAL EFFECTIVE DATE: 05/16/2019 | ARCHIVE DATE: | LAST REVIEW DATE: 05/15/2025 | LAST CRITERIA REVISION DATE: 11/21/2024

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Age Requirement

- 2 years of age or older

Alternative Therapies

- Failure, contraindication, intolerance to **TWO** of the following:
  - Preservative-free artificial tears used every 2–4 hours **and** ocular lubricant ointment at bedtime
  - Topical antibiotics for symptomatic and asymptomatic individuals
  - Corneal or scleral contact lens therapy
  - Autologous serum eye drops or punctal (silicone) plugs

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the U.S. Food and Drug Administration (FDA) (see Definitions section)

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Approval Duration

- 8 weeks per affected eye
- Requests for additional course for recurrence will follow the above criteria

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Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Oxervate (cenegermin-bkbj) is indicated for the treatment of neurotrophic keratitis. Oxervate (cenegermin-bkbj) is a recombinant human nerve growth factor (NGF) that is structurally identical to the NGF protein made in the human body, including in the ocular tissues. NGF receptors are expressed in the anterior segment of the eye (cornea, conjunctiva, iris, ciliary body, and lens), by the lacrimal gland, and by the posterior segment ocular tissues. NGF acts directly on corneal epithelial cells to stimulate growth and survival; it binds to receptors on lacrimal glands to promote tear production, and may support corneal innervation, which is lost in NK.

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Cenegermin-bkbj is a topical solution instilled in the affected eye(s) 6 times a day at 2-hour intervals for 8 weeks. An alarm should be used to assure every 2-hour dosing. Administration of the drug requires 19 steps including connecting a vial adapter to the vial, inserting a pipette into the vial adapter, withdrawing the solution into the pipette, removing the pipette from the adapter, instilling the drug into the affected eye, and tracking each dose on the provided recording card.

Neurotrophic keratitis (NK) is a rare degenerative corneal disease resulting from impaired function of corneal nerves, which can be caused by infections, ocular surface injuries, ocular or neurologic surgeries, and some systemic conditions that can impair corneal sensation. NK is caused by an impairment in the trigeminal nerve (cranial nerve V1) which leads to a decrease (hypoesthesia) in or absence (anesthesia) of corneal sensitivity. The loss of corneal sensation causes progressive damage to the top layer of the cornea, resulting in corneal thinning, ulceration, and perforation in severe cases.

Damage to the cranial nerve may be caused by herpetic keratitis, ophthalmic and neurosurgical procedures, chemical burns, physical injuries, long-term use of contact lenses, chronic use of topical medications, aneurysm, and neoplasm. NK is also associated with diabetes mellitus, multiple sclerosis, and congenital syndromes (e.g., Riley-Day syndrome, Goldenhar-Gorlin syndrome, Möbius syndrome). The most common causes of NK are herpetic corneal infections, surgery for trigeminal neuralgia, and surgery for acoustic neuroma.

The diagnosis of NK is based on the clinical history that may identify conditions associated with trigeminal impairment, presence of persistent epithelial defect (PED) or ulcers and decreased corneal sensitivity. Symptoms during the early stage of the disease may include dryness, photophobia, impaired quality of vision, and reduced blinking.

There is no formal clinical guideline available that addresses treatment. Diagnosis, prognosis, and treatment are based on disease severity. NK is classified into three stages. Stage 1 (mild) is characterized by ocular surface irregularity and reduced vision; stage 2 (moderate) is characterized by a non-healing PED; and stage 3 (severe) exhibits corneal ulceration involving sub-epithelial (stromal) tissue, which may progress to corneal melting and perforation. Early diagnosis and treatment may prevent progression of corneal damage.

Therapy for stage 1 (mild) disease is to prevent epithelial breakdown by administering preservative-free artificial tears and discontinuing all topical and systemic medications associated with ocular surface toxicity. Use of punctal (silicone) plugs may also help increase tear volume.

The goal of treatment for stage 2 (moderate) NK is to promote healing of the epithelial defect and to avoid the development of corneal ulcers. In addition to preservative-free artificial tears and punctal plugs, topical antibiotics are recommended to prevent infections. Autologous serum eye drops, which contain components of natural tears (e.g., growth factors, vitamins, cytokines, and neuromediators) are used.

The aim of treatment at stage 3 (severe) disease is to prevent corneal thinning and perforation. Various surgeries and procedures are available to treat ulcers not responding to medical treatment. Tarsorrhaphy is the most commonly used procedure to promote corneal healing. Alternatives include botulinum-induced ptosis, amniotic membrane transplantation, eyelid closure with tape, patching, and use of the conjunctival flap to cover the corneal surface.

The safety and efficacy of Oxervate (cenegermin-bkbj) compared to vehicle was established in two, 8-week clinical studies in 151 patients with NK. All eye drops in both studies were given six times daily in the affected

eye(s). In the first study, 72.0% of individuals with disease in one eye experienced complete corneal healing with Oxervate (cenegermin-bkbj) vs. 33.3% with vehicle (difference: 38.7% [95% CI: 20.7%, 56.6%]; p < 0.01). In the second study, 65.2% of individuals with disease in both eyes experienced complete corneal healing with Oxervate (cenegermin-bkbj) vs 16.7% with vehicle (difference: 48.6% [95% CI: 24%, 73.1%]; p < 0.01). According to the package label, individuals who were healed after 8 weeks of treatment with Oxervate (cenegermin-bkbj), recurrences occurred in approximately 20% in study 1 and 14% in study 2.

In 2021, an expert panel using a validated methodology (a RAND/UCLA modified Delphi panel) developed consensus on when to screen for and how best to diagnose and treat NK. For all stages of NK, the panel agreed that optimal care should include discontinuing preservative-containing topical medications, when possible. For topical medications that do not have preservative-free alternatives, the panel recommended decreasing the dose if possible. The panel also concluded that for all patients with NK (regardless of stage), optimal treatments (alone or in combination) may include preservative-free artificial tears or ocular lubricants (gels and ointments), punctal occlusion, and autologous serum tears/umbilical cord serum drops/platelet rich plasma drops. For patients with Stage 2 disease, the panel considered cenegermin-bkbj, prophylactic topical preservative-free antibiotics, matrix metalloproteinases inhibitors such as oral tetracyclines (e.g., doxycycline), corneal therapeutic contact lenses, and fresh-frozen self-retained amniotic membrane as additional optimal treatments. For Stage 3 disease, in addition to the treatments recommended in Stage 2, the panel agreed that synthetic tissue adhesive, tarsorrhaphy, amniotic membrane transplant, and corneal neurotization were optimal treatments. The authors also concluded that these recommendations need to be validated with studies that include patient outcomes, as the consensus statements were derived from studies with small sample sizes, observational studies, and experience of clinicians.

In 2022 data from a retrospective, observational case series was published from a single-center setting of 18 patients with diagnosis of stage 2 or 3 NK, who were treated with Oxervate (cenegermin-bkbj) and followed for up to 48 months. In case of recurrence, retreatment with Oxervate (cenegermin-bkbj) was not permitted and patients were treated with conventional management based on clinical findings. At the end of 8-weeks of treatment, all patients had corneal healing. Recurrence of lesion during follow-up was evaluated at 12, 24, 36, and 48 months. Three patients experienced recurrence of persistent epithelial defects (PEDs) within 12 months and one patient experienced recurrence of a corneal ulcer within 36 months. All patients with recurrence of NK were treated with therapeutic contact lens application and topical lubricants and all showed complete corneal healing. Corneal sensitivity, Schirmer tear test, and visual acuity (VA) were recorded at baseline, end of treatment, and at 12, 24, 36, and 48 months. Corneal sensitivity was significantly improved at all timepoints. Significant improvements in visual acuity and tear production were seen at the completion of treatment and at 12, 24, and 36 months when compared to baseline. The authors concluded that a single 8-week treatment regimen of Oxervate (cenegermin-bkbj) eye drops had clinical efficacy that can persist for up to 48 months. The long-term clinical utility of treatment with Oxervate (cenegermin-bkbj) for NK was demonstrated through the low rate of lesion recurrence (4/18 or 22%) along with improvements in corneal sensitivity and tear production.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Stages of NK:

Stage 1	Punctate epithelial staining Decreased tear breakup test Rose bengal staining of inferior palpebral conjunctiva Dellen Gaule spots Stromal scarring
Stage 2	Persistent epithelial defect (PED) Stromal swelling Surrounding rim of loose epithelium Rare anterior chamber reaction
Stage 3	Corneal ulcer Stromal lysis Perforation

Resources:

Oxervate (cenegermin-bkbj) product information, revised by Dompe Farmaceutici S.p.A. 02-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Dana R, Farid M, Gupta PK, et al.: Expert consensus on the identification, diagnosis, and treatment of neurotrophic keratopathy. BMC Ophthalmology (2021) 21:327. Accessed March 13, 2024. Re-evaluated March 06, 2025.

Bruscolini A, Marenco M, Albanese GM, et al.: Long-term clinical efficacy of topical treatment with recombinant human nerve growth factor in neurotrophic keratopathy: a novel cure for a rare degenerative corneal disease? Orphanet Journal of Rare Diseases (2022) 17:57. Assessed March 31, 2024. Re-evaluated March 06, 2025.

Pflugfelder SC, Massaro-Giordano M, Perez VL, et. al.: Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy: A Multicenter Randomized Vehicle-Controlled Pivotal Trial. Ophthalmology 2020 Jan;127 (1):14-26. Accessed April 07, 2021. Re-evaluated March 06, 2025.

Fleeman N, Mahon J, Nevitt S, et. al.: Cenegermin for treating Neurotrophic Keratitis: An evidence review group of a NICE Single Technology Appraisal. PharmacoEconomics - Open (2019) 3:453–461. https://doi.org/10.1007/s41669-019-0138-z Accessed April 07, 2021. Re-evaluated March 06, 2025.

Technology appraisal guidance: Cenegermin for treating neurotrophic keratitis. National Institute for Heath and Care Excellence (NICE) July 18, 2018, nice.org.uk/guidance/ta532. Accessed April 15, 2019. Re-evaluated March 06, 2025.

Bonini, S; Lambiase, A; Rama, P; et al; Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology 2018 Sept; 125(9):1332-1243. Accessed March 06, 2025.

Semeraro F, Forbice E, Romano V, et al. Neurotrophic keratitis. Ophthalmologica. 2014; 231(4):191-197 DOI: 10.1159/000354380. Accessed April 15, 2019. Re-evaluated March 06, 2025.

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clinical Ophthalmology 2014 March 19:8 571–579. Accessed April 07, 2021. Re-evaluated March 06, 2025.