09-J3000-15

Original Effective Date: 12/15/18

Reviewed: 04/09/25

Revised: 05/15/25

Subject: Cenegermin-bkbj (Oxervate®) Ophthalmic Solution

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Cenegermin-bkjl (Oxervate) is a recombinant human nerve growth factor approved by the US Food and Drug Administration (FDA) in August 2018 for the treatment of neurotrophic keratitis. Cenegermin was previously granted orphan drug designation by the FDA for this indication in June 2014. While a specific age is not included in the FDA-approved indication for use, the package labeling states that “the safety and effectiveness of Oxervate have been established in the pediatric population. Use of Oxervate in this population is supported by evidence from adequate and well-controlled trials of Oxervate in adults with additional safety data in pediatric patients from 2 years of age and older.” Neurotrophic keratitis (NK) is a rare degenerative corneal condition that develops in patients who have sustained damage to the trigeminal nerve (via herpetic infection, ocular or neurologic surgeries, chemical burns, abuse of anesthetics, diabetes mellitus, multiple sclerosis, etc.). Once damaged, the nerve's ability to maintain corneal homeostasis is impaired; thereby resulting in decreased corneal sensitivity, impaired tearing reflexes, alterations in the metabolism and vitality of the corneal epithelium and reduced epithelial healing. Treatment with nerve growth factor restores the function of the injured neurons, and subsequently, corneal homeostasis. Cenegermin is the first drug to be approved by the FDA for the treatment of NK.

Neurotrophic keratitis is classified as an orphan disease with an estimated prevalence of less than 5/10,000 individuals. The hallmark of NK is a decrease or absence of corneal sensation. Patients with NK rarely complain of symptoms, probably due to their lack of corneal sensation. An NK classification based on severity was proposed by Mackie, who distinguished three stages. Stage 1 NK is characterized by corneal epithelial changes with dry and cloudy corneal epithelium, presence of superficial punctate keratopathy, and corneal edema. Stage 2 NK is characterized by recurrent and/or persistent corneal epithelial defect (PED) with an oval or circular shape, most frequently localized at the superior half of

the cornea. Stage 3 NK is characterized by corneal ulcer with stromal involvement that may be complicated by stromal melting and progression to corneal perforation. The diagnosis of NK is mainly based on the clinical history of conditions associated with trigeminal impairment, presence of PED or ulcers, and decreased corneal sensitivity. Corneal sensitivity can be measured qualitatively by touching the central and peripheral cornea with a cotton thread or quantitatively using a corneal esthesiometer (via contact or non-contact methods). There are no consensus guidelines that address the management of NK. Goals of treatment are to achieve epithelial healing and prevent progression of corneal damage. Treatment selection should be based on disease severity. The use of preservative-free artificial tears may help improve the corneal surface at all stages of disease severity. Use of topical antibiotic eye drops to prevent infection in eyes with NK at stages 2 and 3 is often recommended. Non-pharmacological treatments include therapeutic corneal or scleral contact lenses in the event of PED to promote corneal epithelial healing. Surgical treatments are reserved for refractory cases. Partial or total tarsorrhaphy (i.e., sewing eyelids together) is the most simple and widespread procedure used to promote corneal healing in the presence of a PED.

The efficacy and safety of cenegermin leading to FDA approval was examined in two randomized, multi-center, double-masked, vehicle-controlled studies (Study NGF0212 and Study NGF0214). Adult patients with Stage 2 or 3 NK were randomized to cenegermin 20 mcg/mL, cenegermin 10 mcg/mL, or vehicle in Study NGF0212, and cenegermin 20 mcg/mL or vehicle in Study NGF0214 dosed 6 times daily in the affected eye(s) for 8 weeks. In study NGF0212, only patients with unilateral disease were enrolled, while in study NGF0214 patients with bilateral disease were treated bilaterally. The mean age was 61 to 65 years. Patient had to have PED or corneal ulceration of at least 2 weeks duration refractory to one or more conventional non-surgical treatments for neurotrophic keratitis. After 8 weeks of treatment, cenegermin 20 mcg/mL as compared with vehicle produced significantly higher rates of complete corneal healing in both NGF02124 (n=47; 65.2% vs. 16.7%, $p<0.01$) and NGF0212 (n=101; 72% vs 33.3%, $p<0.01$). In patients who were healed after 8 weeks of treatment, recurrences occurred in 14% of patients in NGF0214 and 20% of patients in NGF0212. There were no clinically significant changes in mean corneal sensitivity inside the lesion from baseline to 8 weeks in either study. The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1 to 10% of cenegermin patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of cenegermin-bkbj (Oxervate) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “8”):

1. The member has a diagnosis of neurotrophic keratitis (NK) as confirmed by decreased corneal sensitivity (e.g., measured by cotton swab method, Cochet-Bonnet contact esthesiometer, CRCERT-Belmonte non-contact esthesiometer) – documentation of the cornel sensitivity test results must be submitted
2. The member has either of the following NK disease severities ("a" or "b") as determined by slit-lamp examination:
    a. Stage 2 – presence of persistent epithelial defects (PED)
    b. Stage 3 - presence of corneal ulcers
3. **EITHER** of the following ("a" or "b"):
    a. The member's epithelial defect(s) and/or corneal ulcer(s) are refractory to treatment with one or more conventional non-surgical treatments (e.g., preservative-free artificial tears, gels or ointments; discontinuation of preserved topical drops and medications that can decrease corneal sensitivity; therapeutic contact lenses)
    b. The member was previously approved for cenegermin treatment by another health plan **AND** documentation of a health plan-paid claim for cenegermin during the 90 days immediately before the authorization request is submitted
4. The member does **NOT** have **ANY** of the following ("a", "b", or ""c):
    a. Active ocular infection
    b. Active ocular inflammation not related to NK
    c. Severe vision loss with no potential for visual improvement
5. Cenegermin is prescribed by, or in consultation with, an ophthalmologist
6. The member is 2 years of age or older
7. The member has not previously received nerve growth factor (including cenegermin), in the affected eye to receive treatment with cenegermin, for the treatment of an ocular disease in their lifetime*
8. The dosage of cenegermin does not exceed one drop 6 times a day per affected eye for 8 weeks

Approval duration: 12 weeks to allow for 8-week treatment [not to exceed 8 total weeks of continuous treatment including prior treatment for any members already on therapy]

**Members completing an 8-week treatment course of cenegermin initiated while at another health plan are exempt from this requirement.*

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Treatment of neurotrophic keratitis

- The recommended dosage is one drop in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks
- Specific preparation and administration directions can be found the product labeling

Dose Adjustments

- Hepatic impairment - specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.
- Renal impairment - specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- A 0.002% (20 mcg/mL) ophthalmic solution supplied in a weekly carton containing 7 multiple-dose vials in an insulated pack in the Delivery System Kit. The Delivery System Kit contains 8 vial adapters, 45 pipettes, 45 sterile disinfectant wipes, and a dose card.
- Store the weekly carton in the freezer at or below -4°F (-20°C). Dispense the weekly carton in the insulated pack in the Delivery System Kit.
- Within 5 hours of leaving the pharmacy, store the weekly carton in the refrigerator between 36°F to 46°F (2°C to 8°C) for up to 14 days. Opened vials may be stored in the original weekly carton in the refrigerator between 36°F to 46°F (2°C to 8°C) or at room temperature up to 77°F (25°C), for up to 12 hours.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Use with Contact Lens** – contact lenses should be removed before applying cenegermin because the presence of a contact lens (either therapeutic or corrective) could theoretically limit the distribution of cenegermin-bkbj onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.
- **Eye discomfort** - cenegermin may cause mild to moderate eye discomfort such as eye pain during treatment. The patient should be advised to contact their doctor if a more serious eye reaction occurs.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

H16.231	Neurotrophic keratoconjunctivitis, right eye
H16.232	Neurotrophic keratoconjunctivitis, left eye

H16.233	Neurotrophic keratoconjunctivitis, bilateral
H16.239	Neurotrophic keratoconjunctivitis, unspecified eye

ICD-10 Diagnoses Codes That Support Medical Necessity

J3590	Unclassified biologics

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guidelines creation.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Corneal esthesiometry - The measurement of corneal sensation. An esthesiometer or aesthesiometer is a device used to measure sensation. To test for corneal sensation there are qualitative and quantitative methods. The most commonly used qualitative method, is the use of a cotton-tipped applicator. Test all four quadrants of the corneal and record the sensation in each location as normal, reduced, or absent. The most common quantitative method is the handheld Cochet-Bonnet esthesiometer.

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/09/25.

GUIDELINE UPDATE INFORMATION:

12/15/18	New Medical Coverage Guideline.
05/15/19	Review and revision to guideline consisting of updating the description section, position statement, and references.
01/01/20	Revision to guideline consisting of updating the position statement.
05/15/20	Review and revision to guideline consisting of updating the references.
05/15/21	Review and revision to guideline consisting of updating the references.
05/15/22	Review and revision to guideline consisting of updating the references.
05/15/23	Review and revision to guideline consisting of updating the references.

05/15/24	Review and revision to guideline consisting of updating the references.
09/15/24	Review and revision to guideline consisting of revising the position statement approval duration to 12 weeks to allow for the 8-week treatment regimen.
05/15/25	Review and revision to guideline consisting of revising the position statement to allow additional corneal sensitivity tests and updating references.