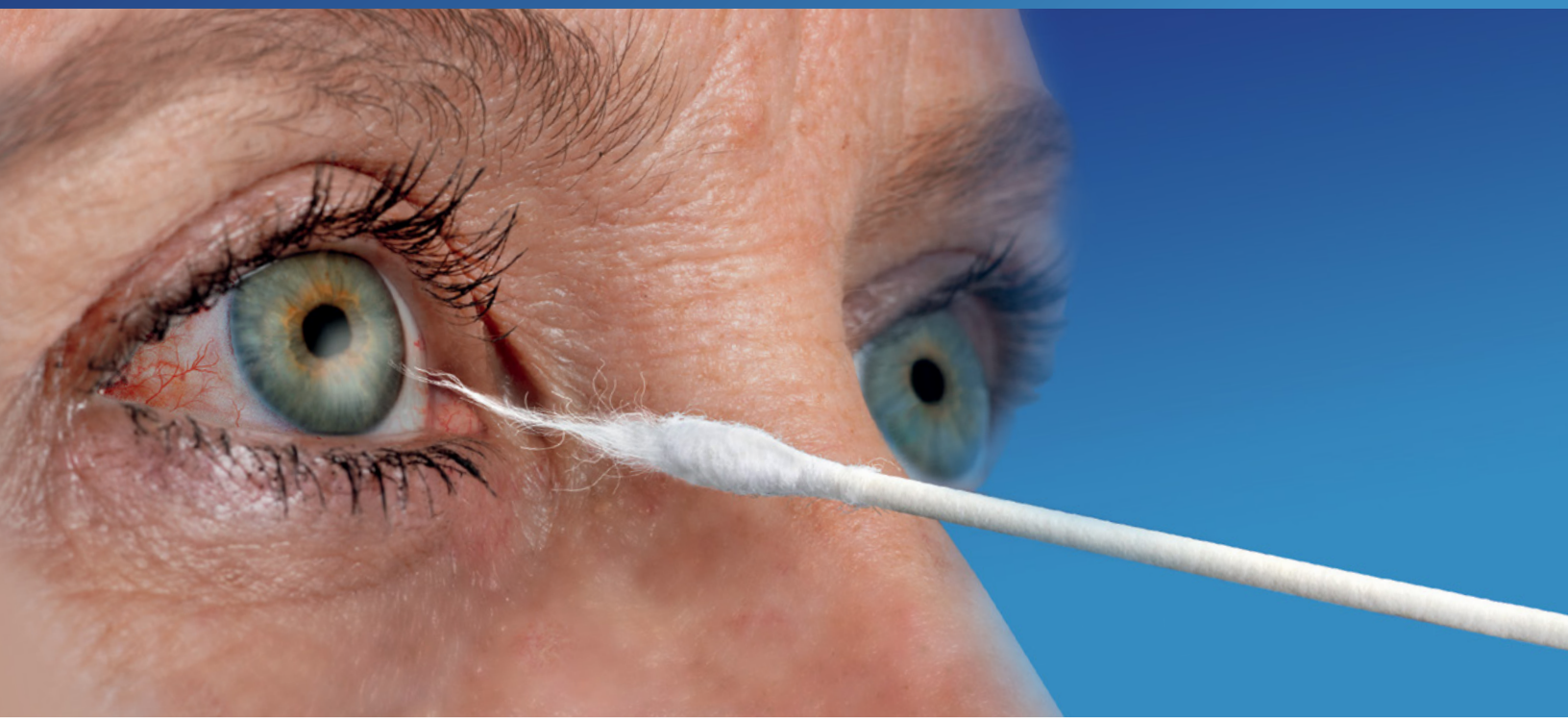
oxervate®
(cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

A guide to neurotrophic keratitis (NK)



Identifying and diagnosing patients with NK in your practice

Please see Important Safety Information throughout and Prescribing Information, including patient information, at OXERVATE.com/prescribing-information.

What is neurotrophic keratitis (NK)?

NK is defined as a rare and degenerative, ocular disease caused by impairment of trigeminal innervation, which leads to a decrease or total loss of corneal sensitivity.[1] Without an early diagnosis and appropriate treatment, NK can progress, with risk of scarring and vision loss.[1-2]

Common etiologies[3]

A number of conditions and procedures can lead to impairment of trigeminal innervation and should prompt suspicion of NK.[3]

- **Herpetic infections**
- **Chronic contact lens use**
- **Chronic ocular surface injury or inflammation**
- **Poorly controlled diabetes**
- **Ocular surgeries**
- **Ocular drug toxicity**
- **Neurosurgical procedures**

Key signs and symptoms[3]

Early stages of NK present similarly to common ocular surface conditions.[3]

- **Loss of corneal sensitivity (hallmark sign)**
- **Dryness**
- **Photophobia**
- **Reduced tear production**
- **Reduced blinking**
- **Blurry vision**

Important Safety Information

Contact lenses should be removed before applying OXERVATE 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.

OXERVATE 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.

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Adverse reactions included corneal deposits, foreign body sensation in the eye, ocular hyperemia (enlarged blood vessels in the white of the eye), swelling (inflammation) of the eye, and increase of tears (1-10% of patients).

INDICATION

OXERVATE (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

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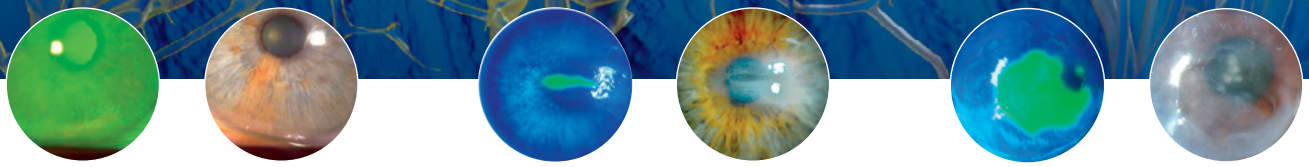
The stages of NK

Fluorescein staining can reveal abnormalities on the surface of the eye and help you assess the severity of NK.[1] Mackie classification defines three stages of NK.[3]



Fluorescein staining | Diffuse white light

STAGE 1 (MILD)

Punctate epithelial keratitis (PEK)[4]

Fluorescein staining | Diffuse white light

STAGE 2 (MODERATE)

Persistent epithelial defect (PED)[3]

Fluorescein staining | Diffuse white light

STAGE 3 (SEVERE)

Corneal ulcers, stromal melting, and perforation[3]

Corneal sensitivity testing is essential to diagnosing NK[3]

Qualitative testing (eg, cotton swab)

Using your fingers or forceps, pull a few fibers from a tight cotton swab to create a wisp that is sharp at the edge.

Quantitative testing (eg, Cochet-Bonnet esthesiometer)

Extend the filament to its full length and touch the cornea with the nylon filament. Retract it incrementally until the patient feels contact.

To test for corneal sensitivity:

1. Ensure testing is performed before anesthetic drops are added
2. Approach the patient's eye from the side using your preferred testing method (qualitative or quantitative)
3. Touch the cornea and look for a blink reaction
4. If using qualitative methods, record sensation as "normal," "partial," or "absent." If using quantitative methods, record the length of the filament. The longer the length at which the patient feels the touch of the filament, the higher the corneal sensitivity
5. Compare to the other eye

It's important to diagnose and treat NK as early as possible before it progresses.[3]

OXERVATE is FDA-approved for the treatment of neurotrophic keratitis.

Learn more about how OXERVATE targets NK at **OXERVATE.com/HCP**.

Important Safety Information (continued)

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution for topical use in the eye: cenegermin-bkbj 0.002% (20 mcg/mL) is a clear, colorless solution in a multiple-dose vial.

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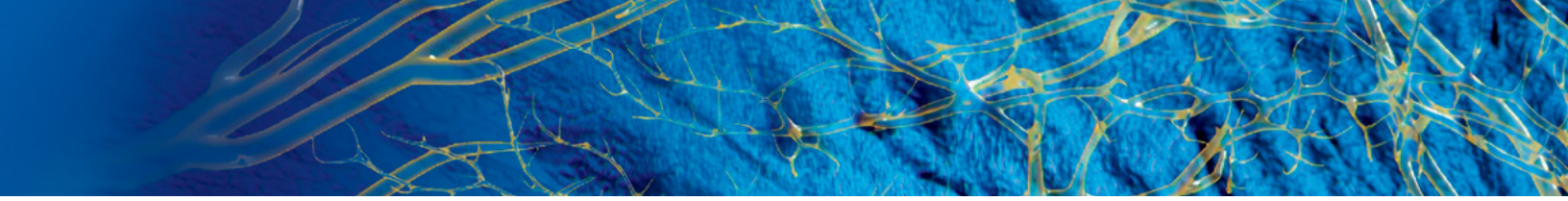

Important Safety Information (continued)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Use With Contact Lenses

Contact lenses should be removed before applying OXERVATE 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

OXERVATE 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.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be compared directly to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In 2 clinical trials of patients with neurotrophic keratitis, a total of 101 patients received cenegermin-bkbj eye drops at 20 mcg/mL at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks. The mean age of the population was 61 to 65 years of age (18 to 95).

The most common adverse reaction in clinical trials that occurred more frequently with OXERVATE was eye pain (16% of patients). Other adverse reactions included corneal deposits, foreign body sensation in the eye, ocular hyperemia (enlarged blood vessels in the white of the eye), swelling (inflammation) of the eye, and increase in tears (1%-10% of patients).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no data from the use of OXERVATE in pregnant women to inform any drug-associated risks.

Administration of cenegermin-bkbj to pregnant rats or rabbits during the period of organogenesis did not produce adverse fetal effects at clinically relevant doses. In a pre- and postnatal development study, administration of cenegermin-bkbj to pregnant rats throughout gestation and lactation did not produce adverse effects in offspring at clinically relevant doses.

Data

Animal Data

In embryofetal development studies, daily subcutaneous administration of cenegermin-bkbj to pregnant rats and rabbits throughout the period of organogenesis produced a slight increase in postimplantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the maximum recommended human ophthalmic dose [MRHOD]). A no-observed-adverse-effect level (NOAEL) was not established for postimplantation loss in either species. In rats, hydrocephaly and ureter anomalies were observed once each in fetuses at 267 mcg/kg/day (1709 times the MRHOD). In rabbits, cardiovascular malformations, including ventricular and atrial septal defects, enlarged heart, and aortic arch dilation, were observed once each in fetuses at 83 mcg/kg/day (534 times the MRHOD). No fetal malformations were observed in rats and rabbits at doses of 133 mcg/kg/day and 42 mcg/kg/day, respectively.

In a pre- and postnatal development study, daily subcutaneous administration of cenegermin-bkbj to pregnant rats during the period of organogenesis and lactation did not affect parturition and was not associated with adverse toxicity in offspring at doses up to 267 mcg/kg/day.

In parental rats and rabbits, an immunogenic response to cenegermin-bkbj was observed. Given that cenegermin-bkbj is a heterologous protein in animals, this response may not be relevant to humans.

Lactation

Risk Summary

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infants, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OXERVATE and with any potential adverse effects on the breastfed infant.

Pediatric Use

The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in pediatric patients 2 years of age and older is supported by evidence from adequate and well-controlled trials of OXERVATE in adults with additional safety data in children.

Geriatric Use

Of the total number of subjects in clinical studies of OXERVATE, 43.5% were 65 years old and older. No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

The FDA-approved product labeling can be found at OXERVATE.com/prescribing-information. You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Dompé at 1-833-366-7387 or Usmedinfo@dompe.com.

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References: 1. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579. **2.** Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232:717-724. **3.** Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131. **4.** Versura P, Giannaccare G, Pellegrini M, Sebastiani S, Campos EC. Neurotrophic keratitis: current challenges and future prospects. *Eye Brain*. 2018;10:37-45.

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