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MODERNOPTOMETRY

Patient Saves in OSD & NK: A Case Series

Jennifer Loh, MD

Justin Schweitzer, OD, FAAO

Chiara Bonzano, MD, PhD, FEBO

Marie Huegel, OD, FAAO

Carolina Mercado, MD

Guillermo Amescua, MD

Carol Karp, MD

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1. Nochez Y, et al. *Invest Ophthalmol Vis Sci*. 2011;52(14):3754.
2. Kursite A and Laganovska G. *J Ophthamol (Ukraine)*. 2023;2:11-5.

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Patient Saves in OSD & NK: A Case Series

INTRODUCTION BY JENNIFER LOH, MD, AND JUSTIN SCHWEITZER, OD, FAAO


What does it mean to save the ocular surface?

Depending on who you ask, and indeed how the question is asked and in what context, it is a question likely to garner a wide array of responses. And so, when we set out to judge the second annual OSD Saves Photo contest, the results of which are presented in the following publication, we had to think about what criteria we would use to select the winners. We wondered whether we should be looking for extraordinary pathology? Whether we should base our decision on how unexpected the final outcome was? Or should we think more closely about the word "save" and look for cases where a patient was spared a seemingly inevitable negative outcome?

We can share with readers that the art of judging a photo contest is highly subjective, and this year, our task was made difficult by the quality of the submissions. It was no easy task to select a few to highlight. Nevertheless, after we had sorted through all the entries, we found four remarkable examples of cases in which the clinician used his or her judgement to arrive at a solution for a complex problem.

The beauty of the criteria we ultimately used for judging, of course, is that we got to define "complex problem" from different vantage points. One case in the following demonstrates the use of a novel therapy for neurotrophic keratitis (NK) in a pediatric patient affected by glioblastoma; the etiology of the NK was certainly complicated by an underlying medical issue. Another case describes the use of an amniotic membrane to facilitate treatment of filamentary keratitis; while this is a clinical entity on the more common side of the spectrum, the particulars of the case underscore the complexity in treating it with the array of options available for use in the clinic. Yet the linkage between these cases and the others in this series is that in the end, the patient was "saved" from irreversible loss of vision, from damage to the ocular structures, or from the life-altering symptoms associated with ocular surface disease.

No matter how you define it, we all know a good "save" when we experience one in the clinic. That is because, thanks to advancements in treatments for clinical entities like NK and other ocular surface disease, the outcomes we used to think were extraordinary are becoming more commonplace. And it is also because clinicians around the world are using those tools in new and creative ways to redefine treatment paradigms in common clinical entities—and we think readers will agree, that much is evident from the cases highlighted in this series. ■

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A Complex Case of Treatment-Resistant Pediatric Neurotrophic Keratitis

BY CHIARA BONZANO, MD, PHD, FEBO

Neurotrophic keratitis (NK) is a degenerative corneal disease resulting from the partial or total impairment of trigeminal innervation.[1] The underlying cause is often unknown, symptoms are often absent, and most cases are identified based on a loss of corneal sensation. However, trauma to the trigeminal nerve could result in impairment.

Treatment of NK is often complicated because interventions are targeted to symptomatic relief. The recent availability of approaches that stimulate regeneration of the trigeminal nerve may offer a new paradigm for treatment.[2-3] This is a case involving the successful treatment of NK that was refractory to conventional treatments in a young patient affected by a diffuse midline glioma.

PRESENTATION

A 7-year-old male child was referred to our cornea service with a diagnosis of NK in the left eye (Figure 1). On examination, the right eye was within normal limits, whereas the left eye showed decreased corneal sensitivity, absent corneal reflex, mild ptosis, and decreased tear production. The medical record indicated a recent diagnosis of pediatric glioma. Symptom reports included frontal headaches, enlarged stride, and slurred speech. One month prior to the development of the NK, he underwent a brainstem biopsy, which revealed a diffuse midline glioma with the H3K27M mutation. He underwent chemotherapy and radiotherapy to treat the brain tumor located in the pons region.

TREATMENT

To treat the NK, we initially started with preservative-free artificial tears, a therapeutic contact lens, and levofloxacin 0.5% eye drops 3 times a day.

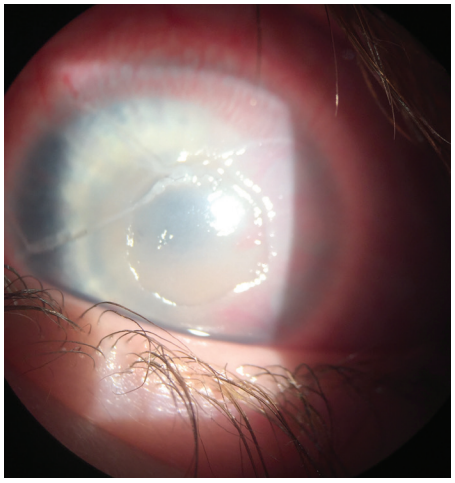

Figure 1. Neurotrophic keratitis in a 7-year-old male child.

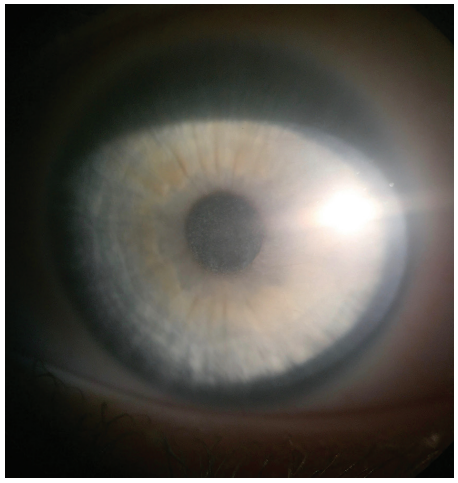

Figure 2. Complete reepithelialization was achieved within 3 weeks of starting Oxervate.

Subsequently, we administered topical autologous serum at a concentration of 40%, 6 times a day for 6 weeks, but there was no improvement in the condition. After receiving approval from the Italian Medicines Agency for pediatric use in this case, we switched to cenegermin-bkbj ophthalmic solution 0.002% (Oxervate; Dompé), which was administered 6 times a day for 8 weeks. Complete reepithelialization was achieved within 3 weeks of starting this treatment (Figure 2).

SUMMARY AND DISCUSSION

In this young patient, the pathophysiology of the NK could be explained by the tumor's infiltration into the cerebellopontine angle, with the resulting impairment manifesting as corneal denervation. The lack of treatment response to palliative measures and efforts to protect and regrow the cornea are perhaps not surprising. Although each measure is a reasonable option to achieve symptomatic relief and/or to attempt repair, none directly address the underlying anatomy. Until recently, treatment approaches for NK have been limited by the absence of treatments targeting the underlying cause.

In this case, corneal denervation resulted in decreased cell metabolism and impaired epithelial mitosis. Cenegermin was effective in restoring corneal integrity. Early diagnosis and prompt management of pediatric NK are mandatory to prevent corneal complications such as perforation and amblyopia. By stimulating nerve regeneration, recombinant human nerve growth factor promotes corneal healing, and may eventually lead to a new standard of care for pediatric patients affected by NK. ■

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Expanding Options for Persistent Corneal Ulcer

BY MARIE HUEGEL, OD, FAAO

A 95-year-old female presented to the clinic with decreased vision in her left eye secondary to a persistent corneal ulcer. Multiple therapies were initiated over several weeks and months to decrease the size of the ulcer, but the therapeutic efforts were unsuccessful. Corneal polymerase chain reaction was performed to ensure there was not an underlying infectious agent causing the corneal ulcer to worsen. She did not have full resolution until topical cenegermin-bkbj ophthalmic solution 0.002% (Oxervate; Dompé) rhNGF was initiated.

PRESENTATION

On initial examination, diffuse superficial punctate keratopathy (SPK) was observed in the left cornea (Figure 1). She did not report any pain or irritation. A 4-mm-horizontal by 2-mm-vertical epithelial defect with an underlying stromal infiltrate of the same size was present. There was no stromal thinning in the left eye at the initial presentation; however, throughout a several week follow-up, the vision fluctuated as the size of the ulcer changed and the stroma became more involved. The size of the ulcer slowly improved by less than one millimeter a week, but the stroma continued to thin under the ulcer (Figure 2).

Other medical history included Type 2 diabetes, hypertension, anemia, and arthritis. She was taking several medications including amlodipine, glipizide, aspirin, buprenorphine transdermal patch, fluticasone propionate, furosemide, gabapentin, AREDs, ropinirole, HCl, and ondansetron.

DIAGNOSIS AND TREATMENT

The patient was diagnosed with a persistent corneal ulcer OS and neurotrophic keratitis (NK) OU. There was minimal improvement with multiple interventions, including bandage contact lenses, punctal plugs, frequent lubrication, and two amniotic membranes. Doxycycline 100mg BID was initiated during the treatment along with mild topical steroids and an antibiotic. The corneal ulcer did not start to heal or improve until an 8-week course of topical cenegermin-bkbj was added to her treatment plan. The degree of improvement is most evident when comparing corneal fluorescein staining before and after treatment (Figure 3).

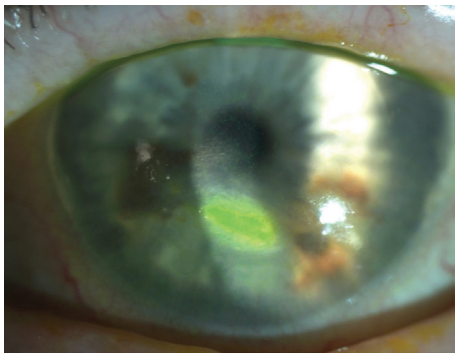

Figure 1. A persistent corneal ulcer in a 95-year-old patient.

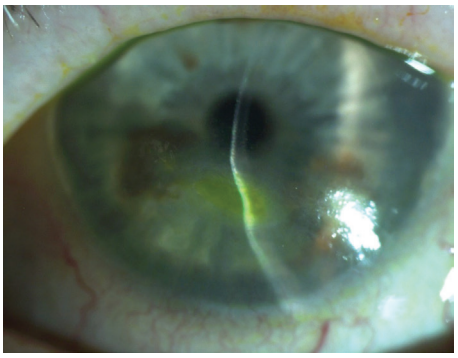

Figure 2. As the size of the ulcer reduced throughout treatment, the stroma became more involved.

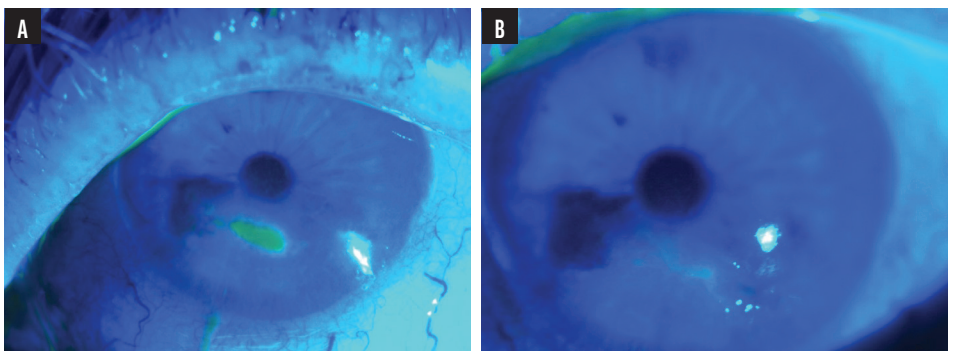

Figure 3. Corneal fluorescein staining before (A) and after (B) treatment with cenegermin-bkbj.

DISCUSSION

The case demonstrates the role of emerging therapeutic options in treating complex corneal ulcers. NK is a difficult to treat clinical entity that has multiple stages which can require different tiers of treatment plans. Because cenegermin-bkbj targets the pathogenesis and underlying cause of NK, there is strong rationale for its use in the treatment of complex and persistent cases. The use of cenegermin-bkbj has been found to be beneficial in all stages of NK.

It is important to first rule out an underlying infectious cause before diagnosing a cornea as neurotrophic. The patient should be monitored closely to ensure no co-infection occurs, and that there is no worsening of signs and symptoms. Patient education is also tremendously important to help prevent further complications or recurrence. Long-term frequent lubrication should be continued even after full resolution of NK to minimize future problems. ■

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SLET Saves the Day

CAROLINA MERCADO, MD; GUILLERMO AMESCUA, MD; AND CAROL KARP, MD



Ocular surface squamous neoplasia (OSSN) is associated with a broad spectrum of clinical presentations, including conjunctival intraepithelial neoplasia, a non-invasive slow-growing tumor from a single cell origin; corneal epithelial dysplasia, or neoplasia, in which corneal epithelial islands are the dominant feature; and squamous cell carcinoma, in which a malignant lesion has gained invasive potential.[1,2] Development of OSSN is multifactorial, involving a mix of environmental factors in a suspectable host.[1] In epidemiologic surveys, OSSN is found more prevalent in geographic areas closer to the equator,[3] suggesting a role for UV light exposure. Indeed, it has been found to most commonly occur in Caucasian men aged 60 to 70 years living close to the equator.[4] Clinically, lesions are primarily found in the interpalpebral fissure where sun exposure is direct.[1] OSSN is the only type of cancer with a comparable response to surgical or medical treatment.[5] The decision is based on tumor location, extension, and patient preference.[6] When treating extensive lesions, the preferred option is chemotherapy, as it treats the whole ocular surface and has a lower risk of limbal stem cell deficiency (LSCD) compared to extensive resections of tissue. We present a case of a patient who had a diffuse corneal OSSN with poor response to topical chemotherapy and developed severe LSCD after tumor excision with cryotherapy.

PRESENTATION

This is a case of a 60-year-old male patient with a diffuse OSSN of the left eye. Medical history included a history of anal warts, sun exposure as a child, and hypertension. For the OSSN, he was treated with two cycles of Interferon eyedrops, two cycles of 5-Fluorouracil eyedrops, and two cycles of Mitomycin C topical chemotherapy without improvement. Due to high out-of-pocket costs and the development of epitheliopathy after 7 months of treatment, he decided to abandon chemotherapy and start Aloe Vera eyedrops, which improved his condition, and chemo reduced the lesion. He then underwent a 6-clock-hour tumor excision, which successfully removed the tumor but resulted in the development of limbal stem cell deficiency (Figure 1).

TREATMENT

After consultation with the patient, he underwent ocular surface reconstruction and simple limbal epithelial transplantation (SLET). Before this procedure, the patient's best corrected visual acuity (BCVA) was counting fingers at 2 feet; 3 months after the procedure, BCVA was 20/40 (Figure 2). A scleral lens will be considered in the future due to severe dry eye and residual corneal irregularity.

SUMMARY

First described in 2012 as a technique to treat limbal stem cell deficiency,[7] SLET involves harvesting healthy limbal cells from a healthy eye for autologous transplantation.[8] SLET may have several advantages relative to other techniques for limbal transplantation.[9,10,11] For

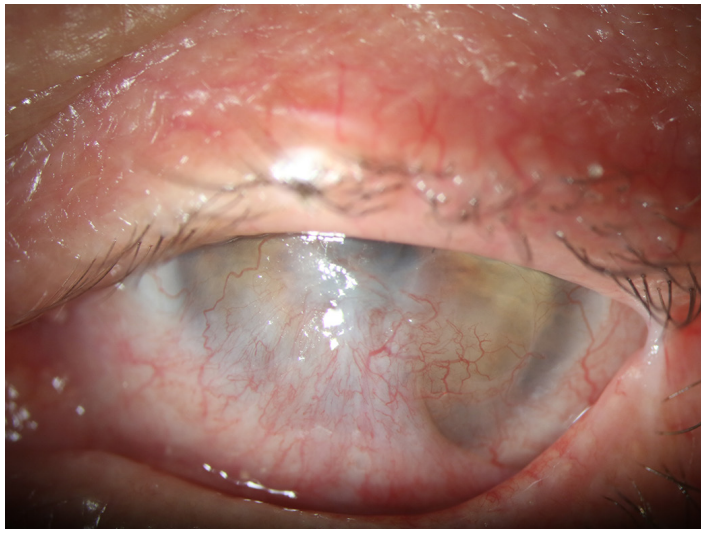

Figure 1. Severe limbal stem cell deficiency in the left eye of a 60-year-old patient.

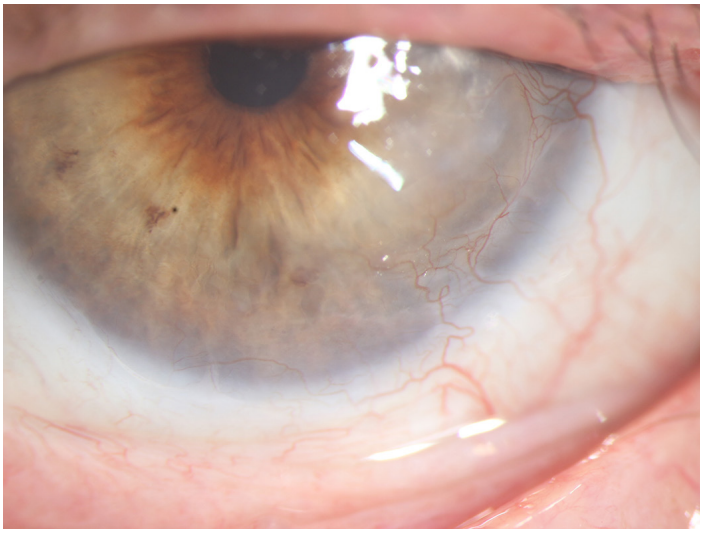

Figure 2. Slit-lamp photography of the left eye, 3 months after SLET.

example, it is a one-stage procedure requiring no particular setup, thus making it cost-effective.[7] SLET requires a smaller donor graft than other limbal stem cell transplantation techniques. Although initially explicitly described for unilateral 360° stem cell deficiency, it has also been successfully used in partial limbal stem cell deficiency. This is an excellent visual and anatomical rehabilitation option for patients with LSCD.

LEARNING POINTS

- Various treatment options for OSSN range from antineoplastics to homeopathic medicine.
- The best option for diffuse OSSN is medical chemotherapy, as wide margins are difficult to identify, but while it is usually successful, it doesn't always work.
- Surgery is another modality that is often successful but doesn't always work and can cause LSCD.
- PRGF membrane is an alternative to minimize corneal scarring in the ocular surface with imminent LSCD.
- Simple limbal epithelial transplantation is an excellent option for ocular surface reconstruction in cases of unilateral LSCD. ■

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Freeze-Dried Amniotic Membrane for Filamentary Keratitis

INRAVA KHASNABISH, OD, FAAO

Filamentary keratitis is a condition in which degenerated epithelial cells and mucous adhere to the corneal surface. It is most likely related to abnormalities of the tear film and/or corneal surface and is known to be a driver and risk factor for numerous ocular surface diseases. Treatment is generally started with topical therapy and lubricating drops. If needed, it may be escalated to include the use of a bandage contact lens and agents to decrease the viscosity of mucous in the tear film.

PRESENTATION

This is a case of a 47-year-old female who presented with painful sandy sensation in both eyes. She had a medical history of dry eye disease and diabetes. On ocular examination, diffuse filaments were evident OU and her visual acuity was 20/50 OD and 20/40 OS. Concomitant medications included Metformin 500 mg. The patient was diagnosed with filamentary keratitis OU and keratoconjunctivitis sicca OU (Figure 1).

DIAGNOSIS AND TREATMENT

The patient was diagnosed with filamentary keratitis and keratoconjunctivitis sicca in both eyes. She was treated with a freeze-dried amniotic membrane with an overlying bandage contact lens, compounded 10% acetylcysteine eye drops TID OD, and Refresh Celluvisc (Allergan, an AbbVie Company) QHS OU. Following initial treatment, the patient's symptoms have subjectively improved and BCVA is 20/25 OD and 20/20 OS. Fluorescein staining showed resolution of the filaments and near resolution of the cornea (Figure 2).

DISCUSSION

A 47-year-old female with diabetes presented with severe ocular pain OU. Ocular examination revealed filamentary keratitis OU, but OD > OS. She was subsequently treated with a freeze-dried amniotic membrane, compounded acetylcysteine, and viscous tears, which resulted in subjective improvement in symptoms and objective improvement in visual acuity. ■

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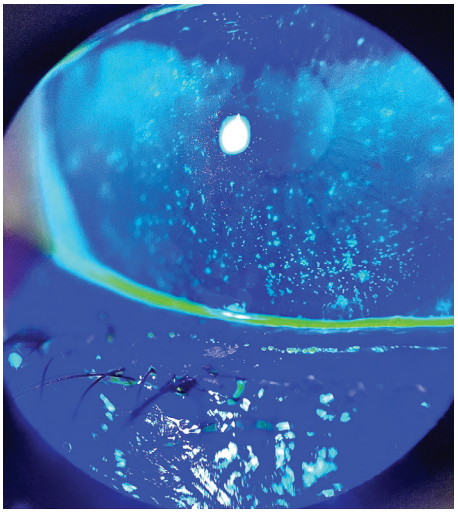

Figure 1. Filamentary keratitis in the right eye of a 47-year-old female.

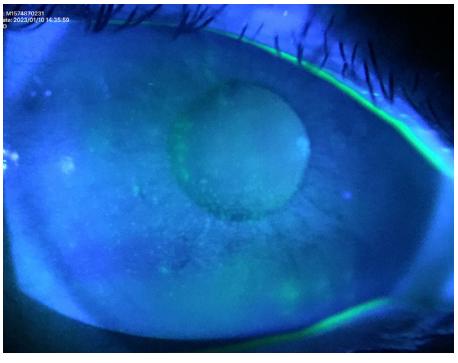

Figure 2. Use of a freeze-dried amniotic membrane resulted in the resolution of the filamentary keratitis.

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

Brief Summary of full Prescribing Information

Consult the full Prescribing Information for complete product information, available at www.oxervate.com/prescribing-information.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

General Dosing Information

Contact lenses should be removed before applying OXERVATE and may be reinserted 15 minutes after administration.

If a dose is missed, treatment should be continued as normal, at the next scheduled administration.

If more than one topical ophthalmic product is being used, administer the eye drops at least 15 minutes apart to avoid diluting products. Administer OXERVATE 15 minutes prior to using any eye ointment, gel or other viscous eye drops.

Recommended Dosage and Dose Administration

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

WARNINGS AND PRECAUTIONS

Use with Contact Lens

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 directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In two 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 majority of the treated patients were female (61%). The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

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.

Lactation

Risk Summary

There are no data on the presence of OXERVATE in human milk, the effects on breastfed infant, 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 any potential adverse effects on the breastfed infant from OXERVATE.

Pediatric Use

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.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin-bkbj.

Impairment of fertility

Daily subcutaneous administration of cenegermin-bkbj to male and female rats for at least 14 days prior to mating, and at least 18 days post-coitum had no effect on fertility parameters in male or female rats at doses up to 267 mcg/kg/day (1709 times the MRHOD).

In general toxicology studies, subcutaneous and ocular administration of cenegermin-bkbj in females was associated with ovarian findings including persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses greater than or equal to 19 mcg/kg/day (119 times the MRHOD).

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* Resolution was evaluated in clinical trials as complete corneal healing, defined as the absence of staining in the lesion area and no persistent staining in the rest of the cornea after 8 weeks of treatment and as <0.5-mm lesion staining at 48-week follow-up.[1-3]

† Key study findings were after 8 weeks of treatment, 6 times daily. REPARO (Study NGF0212): 52 European patients with neurotrophic keratitis (NK) in 1 eye per group; 72% of patients completely healed; vehicle response rate 33.3%. Study NGF0214: 24 US patients with NK in 1 or both eyes per group; 65.2% completely healed; vehicle response rate 16.7%.[2,3]

Important Safety Information

WARNINGS AND PRECAUTIONS

Use with Contact Lens

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

In clinical trials, 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 OXERVATE patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing.

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Lactation

The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for OXERVATE, and any potential adverse effects on the breastfed infant from OXERVATE.

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.

INDICATION

OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) is indicated for the treatment of neurotrophic keratitis.

DOSAGE AND ADMINISTRATION

Instill one drop of OXERVATE in the affected eye(s), 6 times a day at 2-hour intervals for eight weeks.

To report ADVERSE REACTIONS, contact Dompé U.S. Inc. at 1-833-366-7387 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the Brief Summary of full Prescribing Information for OXERVATE on the following page.

References: 1. OXERVATE® (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA; Dompé U.S. Inc.; 2019. **2.** Bonini S, et al. *Ophthalmology*. 2018;125:1332-1343. **3.** Pflugfelder SC, et al. *Ophthalmology*. 2020;127:14-26. **4.** Data on File. Clinical Study Report (NGF0212). Dompé U.S. Inc., 2016.

See more clinical data
OXERVATE.com/hcp

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