oxervate™

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

FULL PRESCRIBING INFORMATION

Dompé

FULL PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OXERVATE safely and effectively. See full prescribing information for OXERVATE.

OXERVATE™ (cenegermin-bkbj) ophthalmic solution for topical ophthalmic use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis. (1)

----------DOSAGE AND ADMINISTRATION----------
One drop of OXERVATE in the affected eye(s), 6 times per day at 2-hour intervals, for eight weeks. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution: cenegermin-bkbj 0.002% (20 mcg/mL) in a multiple-dose vial. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence >5%) are eye pain, ocular hyperemia, eye inflammation and increased lacrimation. (6.1)

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

1. INDICATIONS AND USAGE

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

2. DOSAGE AND ADMINISTRATION

2.1 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.

2.2 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.

2.3 Preparation for Administration

Remove the weekly cartons of OXERVATE from the insulated container and store it for up to 14 days in a refrigerator (no later than 5 hours from when you receive the medicine from your pharmacy). OXERVATE is stored in a freezer at the pharmacy. If treatment is started immediately after receiving the weekly carton, wait until the first vial is thawed (this could take up to 30 minutes when kept at room temperature up to 77°F (25°C)). Do not shake the vial.

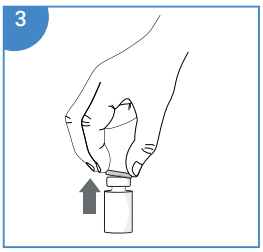
Follow Steps 1 to 19 each day you use OXERVATE:

Take an individual vial of OXERVATE from the refrigerator in the morning and prepare it in the following way:

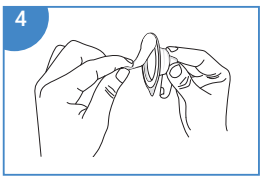
Step 1. Wash your hands.

Step 2. If you wear contact lenses, take them out before using OXERVATE.

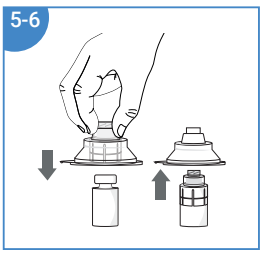
Step 3. Remove the plastic flip-off cap from the vial.



Step 4. Peel-off the back of the vial adapter blister pack.



Step 5. Without removing the vial adapter from its blister pack, connect it to the vial by firmly pushing it down until it snaps into place over the neck of the vial. The spike of the vial adapter should pierce through the vial's rubber stopper. After the vial adapter has been connected correctly, do not remove it from the vial.



Note: After the vial adapter is connected to the vial, OXERVATE can be stored in the refrigerator between 36°F to 46°F (2°C to 8°C) for **up to 12 hours.**

If needed, the OXERVATE with the connected vial adapter may be stored at room temperature up to 77°F (25°C).

Step 6. Remove and throw away the packaging of the vial adapter.

The multi-dose vial of OXERVATE is now ready for use (1 drop in the affected eye every 2 hours six times a day).

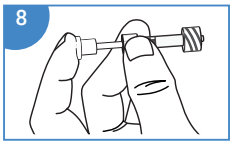
To withdraw and give each dose of OXERVATE, follow the Steps 7 to 19:

Step 7. Take a single sterile disinfectant wipe and gently clean the surface of the valve on the connector part of the vial adapter.

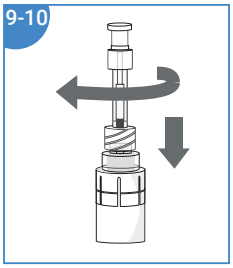
After cleaning, wait for about 1 minute to allow the valve to dry.

Step 8. Remove a pipette from its protective packaging.

Step 9. Screw the pipette (clockwise) into the connector part of the vial adapter.

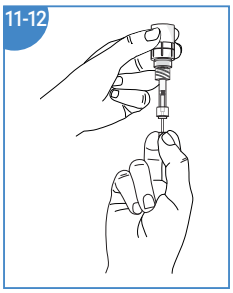


Step 10. Make sure that the pipette plunger is pushed all the way down.

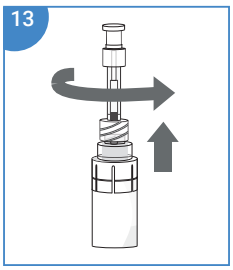


Step 11. Turn the vial upside-down with the pipette still connected. Gently pull the plunger until it stops, to draw the eye drop solution into the pipette. Make sure the plunger has reached the stop point.

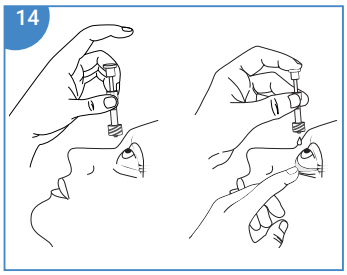
Step 12. Check the pipette to make sure it contains the eye drop solution. Air bubbles may cause blockage and prevent the pipette from filling properly (especially the first time you withdraw the eye drop solution). If the pipette is empty, keep the vial with the connected pipette upside-down, push the plunger all the way in and pull it out again.



Step 13. After the pipette has been correctly filled, unscrew the pipette from the connector part of the vial adapter (counter-clockwise). Pull the pipette straight up to remove it.



Step 14.

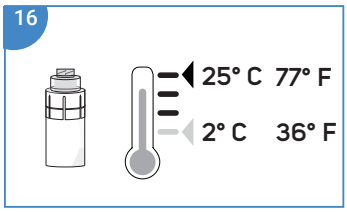


- Sit or lie down to steady yourself when you instill OXERVATE.
- Holding the pipette, pointing down, between your middle finger and thumb, tilt your head back and position the pipette above your affected eye.
- With your other hand, pull down your lower eyelid, increasing the space between the inner eyelid and the eyeball (the conjunctival fornix).
- Gently push the plunger down until at least a drop is released into the conjunctival fornix.
- Make sure you do not touch your eye with the tip of the pipette.
- With your head still tilted back, blink a few times so that the medicine covers the surface of your eye.

Step 15. Throw away the used pipette right away after use, even if there is still eye drop solution left in it.

If you miss your eye and there is no longer eye drop solution in the pipette, try again, using a new pipette and wipe (See Steps 7 to 14).

Step 16. After each use throughout the day, place the vial back in the refrigerator or keep it below 77°F (25°C) for the rest of the day, with the vial adapter still connected.

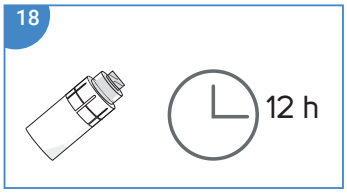


Step 17. Repeat from Step 7 to Step 16 every 2 hours 6 times a day, using a new sterile disinfectant wipe and a new pipette each time.

If you use drops in both eyes, repeat the above instructions for your other eye using a new pipette. You will need to use 2 vials each day.

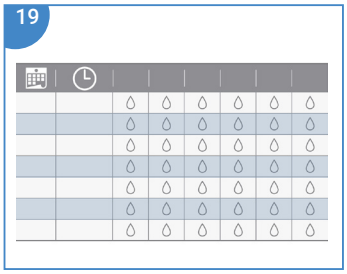
Store the vial below 77°F (25°C) throughout the day. You can also store the vial in the refrigerator but do not freeze the vial.

Step 18. Throw away the used vial at the end of each day even if there is still some eye drop solution left in it. Throw away the vial no later than 12 hours from the time you connected the vial adapter to it.



Step 19. Track each time you instill an eye drop of OXERVATE on the weekly Dose Recording Card provided with the delivery system.

This will allow you to track your 6 doses each treatment day, the date of the first use of the weekly supply and the time of the vial opening (which is when you connect the vial adapter to the vial) during the week.



To make sure accurate dosing every 2 hours, you may want to set an alarm as a reminder for dosing.

3. DOSAGE FORMS AND STRENGTHS

Ophthalmic solution: cenegermin-bkbj 0.002% (20 mcg/mL) as a clear, colorless solution in a multiple dose vial.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 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.

5.2 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.

6. ADVERSE REACTIONS

6.1 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.

8. USE IN SPECIFIC POPULATIONS

8.1 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 post-implantation loss at doses greater than or equal to 42 mcg/kg/day (267 times the MRHOD). A no observed adverse effect level (NOAEL) was not established for post-implantation loss in either species. In rats, hydrocephaly and ureter anomalies were observed each in one 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 each in one 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.

8.2 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.

8.4 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 *[see Clinical Studies (14)]*.

8.5 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.

11. DESCRIPTION

OXERVATE ophthalmic solution contains cenegermin-bkbj, a recombinant form of human nerve growth factor produced in *Escherichia coli*.

Cenegermin-bkbj contains 118 amino acids. Cenegermin-bkbj has a relative molecular mass of 13,266 Daltons and the following molecular formula: $C_{583}H_{908}N_{166}O_{173}S_{8}$. OXERVATE (cenegermin-bkbj) is a clear, colorless sterile solution with a pH of 7.0-7.4 and osmolarity 280-320 mOsm/kg for topical ophthalmic use.

Each mL contains **Active:** 20 mcg of cenegermin (0.002% w/v); **Inactives:** disodium hydrogen phosphate anhydrous (2.87 mg), hydroxypropylmethyl cellulose (1.0 mg), L-methionine (0.01 mg), mannitol (12.22 mg), polyethylene glycol 6000 (10.0 mg), sodium dihydrogen phosphate dihydrate (1.22 mg), trehalose dihydrate (47.03 mg), Water for Injection, USP, and hydrochloric acid and/or sodium hydroxide to adjust pH.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nerve growth factor is an endogenous protein involved in the differentiation and maintenance of neurons, which acts through specific high-affinity (i.e., TrkA) and low-affinity (i.e. p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.

12.2 Pharmacodynamics

No pharmacodynamic studies have been conducted in humans.

12.3 Pharmacokinetics

Systemic exposure to cenegermin-bkbj was evaluated by measuring serum nerve growth factor (NGF) concentrations in 20 healthy subjects who received single and multiple (up to six times a day) administration of one drop (35 µL) OXERVATE (0.70 µg of cenegermin-bkbj/administration). The study also included a placebo arm in 10 healthy subjects who received vehicle only.

At baseline/pre-dose, 17 out of the 20 subjects in the OXERVATE treatment arm had serum NGF concentrations below the limit of assay quantification (LLOQ <15 pg/ml) and the remaining three subjects had serum NGF concentrations ranging from120 pg/ml to 503 pg/ml.

At baseline/pre-dose, 8 of the 10 subjects in the placebo arm had serum NGF concentrations below the limit of assay quantification (LLOQ <15 pg/ml) and the remaining two subjects had serum NGF concentrations ranging from 15 pg/ml to 116 pg/ml.

Overall, there was no apparent relationship between OXERVATE treatment and serum NGF concentrations.

13. NONCLINICAL TOXICOLOGY

13.1 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 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).

14. CLINICAL STUDIES

The efficacy and safety of OXERVATE for the treatment of neurotropic keratitis was studied in a total of 151 patients, evaluated in two 8-week, randomized, multi-center, double-masked, vehicle-controlled studies. Patients were randomized to OXERVATE, cenegermin-bkbj 10 mcg/mL, or vehicle in Study NGF0212, and OXERVATE 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 (18-95). The majority of patients were female (approximately 61%).

Table 1 below summarizes the results for complete corneal healing defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment.

Table 1. Percentage of Patients with Complete Corneal Healing at Week 8

Study	OXERVATE	Vehicle	Treatment Difference* (95% CI)
NGF0214	15/23 (65.2%)	4/24 (16.7%)	48.6% (24%, 73.1%)
NGF0212	36/50 (72.0%)	17/51 (33.3%)	38.7% (20.7%, 56.6%)

Patients without any post-baseline measurements were excluded from the analysis.
* p-value < 0.01 for both studies.

In patients who were healed after 8 weeks of treatment with OXERVATE, recurrences occurred in approximately 20% of patients in Study NGF0212 and 14% of patients in Study NGF0214.

The results of the mean change from baseline in corneal sensitivity inside the lesion after 8 weeks of treatment are summarized descriptively in Table 2. The mean changes in corneal sensitivity were not clinically significant in either study.

Table 2: Mean Corneal Sensitivity inside the Lesion: Baseline and Change from Baseline at Week 8.

Study	Visit*	OXERVATE	Vehicle	Treatment Difference** (95% CI)
NGF0214	Baseline	0.8 (1.19)	0.6 (0.70)	
	Change from baseline at Week 8	1.6 (0.26)	0.7 (0.25)	0.9 (0.2, 1.7)
NGF0212	Baseline	1.1 (1.34)	1.0 (1.19)	
	Change from baseline at Week 8	1.1 (0.23)	0.8 (0.23)	0.3 (-0.4, 0.9)

Change from baseline in corneal sensitivity inside the lesion was analyzed using an analysis of covariance model adjusting for baseline values. Patients without any post-baseline measurements were excluded from the analysis.
* Mean (standard deviation) are presented at baseline; least squared means (standard error) are presented at Week 8
** NGF0214: OXERVATE, n = 21; Vehicle, n = 23
NGF0212: OXERVATE, n = 48; Vehicle, n = 47

16. HOW SUPPLIED/STORAGE AND HANDLING

OXERVATE (cenegermin-bkbj) ophthalmic solution, 0.002% (20 mcg/mL), is a sterile, preservative-free clear, colorless solution in a multiple-dose vial, closed with a rubber stopper (not made with natural rubber latex), and an aluminum overseal with a polypropylene flip-off cap.

OXERVATE is supplied in weekly cartons containing 7 multiple-dose vials (NDC 71981-020-07) in an insulated pack with the Delivery System Kit (NDC 71981-001-01). The Delivery System Kit contains 8 vial adapters, 45 pipettes, 45 sterile disinfectant wipes, and 1 Dose Recording Card.

Pharmacy Storage

Store the weekly cartons in the freezer at or below -4°F (-20°C). Supply the weekly cartons in an insulated pack in combination with the Delivery System Kit.

Patient Storage

Within 5 hours of delivery, store the weekly carton(s) containing OXERVATE vials in the refrigerator between 36°F to 46°F (2°C to 8°C) for up to 14 days. A vial opened for daily use 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 *[see Dosage and Administration (2.1)]*. Do not refreeze the vials. Do not shake the vials. Discard the opened vial after 12 hours even if there is still some solution left inside.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Handling the Vials and the Delivery System

Advise patients that OXERVATE should be administered using the vial adapters, pipettes, and sterile disinfectant wipes provided in the Delivery System Kit and according to the instructions *[see Dosage and Administration (2)]*. One individual pipette should be used per application.

Use with Contact Lenses

Advise patients that contact lenses should be removed before applying OXERVATE and to wait 15 minutes after instillation of the dose before reinserting the contact lenses into the eyes *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

Use with other topical products

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

Delayed or Missed Dose

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

Storage Information

Instruct the patient to remove the weekly carton(s) containing 7 OXERVATE vials from the insulated pack within 5 hours of receiving it from the pharmacy and store the weekly carton(s) in the refrigerator [36°F to 46°F (2°C to 8°C)].

Instruct the patient to only remove the number of OXERVATE vials from the weekly carton required for use over the course of a single day. Do not shake the vial.

Once opened, the vial can be kept in the original weekly carton in the refrigerator between 36°F to 46°F (2°C to 8°C) for up to 12 hours or at room temperature up to 77°F (25°C), but must be used within 12 hours. After 12 hours, advise patients to discard the vial with any unused amount.

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Dompé farmaceutici S.p.A.
Via Campo di Pile
67100 L'Aquila, Italy
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