PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**OXERVATE**™

cenegermin

Ophthalmic Solution, 0.002% (20 mcg/mL) Topical Eye Drops

Preservative-free

Professed Standard

ATC code: S01XA24

Dompé farmaceutici S.p.A.
Via Santa Lucia, 6
Milano
Italy
20122
www.dompe.com/en/

Imported/Distributed by:
C.R.I., Dundas, Ontario
L9H 7P3

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RECENT MAJOR LABEL CHANGES

Not Applicable

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

OXERVATE (cenegermin) ophthalmic solution is indicated for the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of OXERVATE have not been established in pediatric patients.

No clinical data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

OXERVATE (cenegermin) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation.

This also includes any other non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging of the Product Monograph.

3 DOSAGE AND ADMINISTRATION

3.1 General Dosing Considerations

- Treatment should be initiated and supervised by an ophthalmologist or a healthcare professional qualified in ophthalmology.
- Eye infections should be treated and resolved prior to beginning OXERVATE treatment (See Section 7, WARNINGS AND PRECAUTIONS, Ophthalmologic, *Eye infections*).
- Patients should be instructed to remove contact lenses before applying OXERVATE and to wait 15 minutes before reinsertion of contact lenses (See Section 7, WARNINGS AND PRECAUTIONS, Ophthalmologic, *Use with Contact Lens*).
- Other topical ophthalmic products may be used during treatment with OXERVATE (cenegermin) when used at least 15 minutes apart, to avoid diluting the other products, with the exception of agents known to inhibit epithelial healing (See Section 7, WARNINGS AND PRECAUTIONS, Ophthalmologic, *Use of corticosteroids or eye drops containing preservatives*). If eye ointment, gel or other viscous eye drops are used, OXERVATE should be administered first. No dedicated studies have been performed to investigate interactions between OXERVATE and other ophthalmic products.

3.2 Recommended Dose and Dosage Adjustment

Instill one drop of OXERVATE in the conjunctival sac of the affected eye(s), 6 times a day at intervals of 2 hours between drops, starting from the morning and within 12 hours. Treatment should be continued for eight weeks.

No dose adjustment is required in patients 65 years of age and older.

OXERVATE has not been studied in patients with hepatic or renal impairment. However, no dose adjustment is considered necessary in these populations.

Health Canada has not authorized an indication for pediatric use.

3.3 Administration

OXERVATE should only be administered using the associated delivery system (vial adapter and pipettes) (See Section 11 STORAGE, STABILITY AND DISPOSAL). An individual pipette should be used per eye drop application. For full instructions, refer to the patient medication information.

Patients will receive a weekly carton containing 7 multi-dose vials of OXERVATE, which can be stored in a refrigerator for up to 14 days until the day of use. Patients will also receive a separate kit of vial adapters, pipettes and disinfectant wipes.

To decrease the risk of introducing microbial contamination, it is important for patients to carefully follow the instructions for cleaning of hands and materials during handling, assembly, and storage of the vial, vial adapter, and pipettes.

3.4 Missed Dose

If a dose is missed, treatment should be continued as normal, at the next scheduled administration. The missed dose can be administered later, within the 12 hours shelf-life of the daily vial. Patients should be advised not to instill more than 1 drop in the affected eye(s) during any administration.

4 OVERDOSAGE

A topical overdose is not likely to occur or to be associated with toxicity (See Section 8.4 Post-Market Adverse Reactions). A topical overdose of OXERVATE may be flushed from the eye(s) with lukewarm water.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Ophthalmic solution/ 0.002% (20 mcg of cenegermin per mL)	disodium hydrogen phosphate anhydrous, hydrochloric acid, hydroxypropylmethyl cellulose, L-methionine, water for injections, mannitol, nitrogen, polyethylene glycol 6000, sodium dihydrogen phosphate dihydrate, sodium hydroxide, trehalose dihydrate

OXERVATE is supplied in sterile, preservative-free multi-dose Type I glass vial, closed with a rubber stopper (not made with natural rubber latex), and an aluminum overseal with a polypropylene flip-off cap, containing 1.0 mL of solution, 7 vials per carton.

OXERVATE should only be used with specific vial adapters and disposable devices (pipettes) that are provided in a separate kit from the weekly OXERVATE carton.

Delivery System Weekly Kit: 7 vial adapters (i.e. 1 per day), 42 pipettes (i.e. 6 per day) and 42 disinfectant wipes (i.e. 6 per day) sufficient to administer the medicinal product for one week are provided as a separate kit, together with a dose recording card. Extra adapter (1), pipettes (3) and wipes (3) are provided as spares.

6 DESCRIPTION

OXERVATE (cenegermin ophthalmic solution 0.002% [20 mcg/mL]) contains cenegermin, a recombinant form of human nerve growth factor produced in *Escherichia coli*. Cenegermin contains 118 amino acids and 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 is a clear, colorless sterile preservative-free solution with a pH of 7.0-7.4 and osmolality 280-320 mOsm/kg. [See 13 PHARMACEUTICAL INFORMATION]

7 WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

Animal studies have not been conducted to determine the carcinogenic and mutagenic potential of cenegermin. As a growth factor, cenegermin has the potential to affect neoplasms. See Section 7 WARNINGS AND PRECAUTIONS Ophthalmologic, *Ocular neoplasms*.

Driving and Operating Machinery

OXERVATE (cenegermin) may cause temporary blurred vision or other visual disturbances that may affect the ability to operate a vehicle or machine (See Section 8 ADVERSE REACTIONS). If blurred vision occurs at instillation, instruct the patient to wait until the vision clears before

driving or using machines.

Ophthalmologic

Risk of corneal melting or impending perforation
It is important that the risk of corneal melting or impending perforation, and the need to undergo emergency surgery or another procedure is assessed before starting therapy with OXERVATE. OXERVATE should not be used in patients requiring immediate surgery.

Eye reactions
OXERVATE may cause mild to moderate eye discomfort, such as eye pain. The patient should be advised to contact their doctor in case of concern or a more severe eye reaction.

Use of corticosteroids or eye drops containing preservatives
Use of ophthalmic topical agents known to inhibit epithelial healing, including corticosteroids or eye drops containing preservatives such as benzalkonium chloride, polyquaternium-1, benzododecinium bromide, cetrimide and other quaternary ammonium derivatives, should be avoided during treatment of neurotrophic keratitis, as they could interfere with corneal healing.

Eye infections
Infections in the affected eye(s) should be treated and resolved before use of OXERVATE. Should an eye infection occur during treatment, OXERVATE should be suspended until infection resolution.

Ocular neoplasms
Cenegermin may theoretically affect ocular neoplasms, as it is a growth factor. OXERVATE should be used with caution in patients with ocular neoplasms. It is recommended that these patients continue to be monitored for cancer progression during and after treatment with this medicinal product.

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 onto the area of the corneal lesion. Lenses may be reinserted 15 minutes after administration.

Sexual Health
Reproduction/Fertility
There are no data on the effects of cenegermin on human fertility. [See Section 15 NON-CLINICAL TOXICOLOGY for fertility studies in animals.]

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from the use of OXERVATE in pregnant women to inform of any drug associated risks. [See Section 15 NON-CLINICAL TOXICOLOGY for animal reproductive studies.]

7.1.2 Breast-feeding

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk, precaution should be exercised.

7.1.3 Pediatrics

Pediatrics (<18 years of age):

No clinical data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

No overall differences in safety or effectiveness were observed between the elderly and younger adult patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

A total of 530 adult subjects have been exposed to cenegermin eye drops (at different formulations, dosages and treatment periods) in clinical trials investigating different conditions (i.e. neurotrophic keratitis, and other ocular pathologies as well as healthy volunteers). This includes 54.9% (n=291) subjects who received cenegermin eye drops containing the same ingredients of OXERVATE (or higher quantities). In this patient population, the majority of adverse reactions were ocular events (91.6% in the cenegermin group; 81.5% in vehicle group), with the most common ocular adverse reactions reported in ≥ 5% of patients being ocular discomfort and eye pain, followed by photophobia.

A total of 108 moderate to severe neurotrophic keratitis patients received cenegermin eye drops at 0.002% (20 mcg/mL) at a frequency of 6 times daily in the affected eye(s) for a duration of 8 weeks, in two double-blinded vehicle-controlled clinical studies (NGF0212 [Phase I and II segments] and NGF0214). One of these studies used the commercial formulation of OXERVATE, which contains the antioxidant L-methionine.

During the controlled treatment periods (NGF0212 [Phase I and II segments] and NGF0214), adverse events occurred in 64.6% of OXERVATE-treated and 52.5% of vehicle-treated patients, serious adverse events occurred in 14.6% of OXERVATE-treated and 12.5% of vehicle-treated patients, adverse events leading to discontinuation occurred in 18.3% of OXERVATE and 12.5% of vehicle patients. Common adverse events from the Phase 2 studies are found in Table 2.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In the two Phase 2 clinical trials conducted in patients with moderate to severe neurotrophic keratitis, the mean age of the population ranged from 61.4 to 65.2 years of age (range 18 to 95 years of age), composed of approximately 60% females, 89.4% white and 3.7% black patients.

Table 2: Summary of Common Adverse Reactions occurring in ≥5% of Oxervate-treated patients with moderate to severe NK and more commonly in patients receiving Oxervate than vehicle during the 8-week vehicle-controlled treatment period of two Phase 2 clinical trials

	Phase II segment NGF0212[1]		**NGF0214[2]**	
System Organ Class/ Preferred Term	**Vehicle (N=52)**	**rhNGF 20 mcg/mL (N=52)**	**Vehicle (N=24)**	**rhNGF 20 mcg/mL (N=23)**
Any Adverse Event, n (%)	**20 (38.5%)**	**27 (51.9%)**	**18 (75.0%)**	**21 (91.3%)**
Eye disorders	**16 (30.8%)**	**13 (25.0%)**	**14 (58.3%)**	**18 (78.3%)**
Cataract	0	0	0	3 (13.0%)
Corneal epithelium defect	1 (1.9%)	0	2 (8.3%)	3 (13.0%)
Corneal thinning	0	0	2 (8.3%)	2 (8.7%)
Eye inflammation	0	1 (1.9%)	2 (8.3%)	3 (13.0%)
Eye pain	4 (7.7%)	5 (9.6%)	2 (8.3%)	7 (30.4%)
Foreign body sensation in eyes	1 (1.9%)	0	0	2 (8.7%)
Lacrimation increased	1 (1.9%)	0	1 (4.2%)	4 (17.4%)
Ocular discomfort	1 (1.9%)	0	2 (8.3%)	2 (8.7%)
Ocular hyperemia	1 (1.9%)	1 (1.9%)	1 (4.2%)	4 (17.4%)
Photophobia	1 (1.9%)	0	2 (8.3%)	2 (8.7%)
Visual acuity reduced	2 (3.8%)	3 (5.8%)	5 (20.8%)	5 (21.7%)
General disorders and administration site conditions	**7 (13.5%)**	**2 (3.8%)**	**6 (25.0%)**	**4 (17.4%)**
Sensation of foreign body	0	0	2 (8.3%)	2 (8.7%)
Investigations	**1 (1.9%)**	**2 (3.8%)**	**2 (8.3%)**	**3 (13.0%)**
Intraocular pressure increased	0	1 (1.9%)	2 (8.3%)	3 (13.0%)

[1] Drug formulation used in NGF0212 did not contain the excipient L-methionine.
[2] Drug formulation used in NGF0214 was the commercial formulation, which contains L-methionine.

In the two Phase 2 clinical trials noted above, there were 10.6% OXERVATE-treated and 17.1% vehicle-treated patients that experienced any form of disease progression (including related preferred terms such as corneal epithelium/epithelial defect, corneal abscess, ulcerative keratitis, corneal erosion, and neurotrophic keratopathy) during controlled treatment. In the two Phase 2 clinical trials noted above, there were 7.7% OXERVATE-treated patients that experienced any form of disease progression (including related preferred terms such as corneal epithelium/epithelial defect, corneal abscess, ulcerative keratitis, corneal erosion, and neurotrophic keratopathy) during uncontrolled treatment. In the follow-up period, there were 15.7% OXERVATE-treated and 5% vehicle-treated patients that experienced disease progression or recurrence under the above-noted preferred terms.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions occurred at a frequency below 5% in patients treated with OXERVATE (with or without methionine) during the controlled treatment period of the Phase 2 trials:

- Blood and lymphatic system disorders: Neutropenia
- Cardiac disorders: Arrhythmia
- Eye disorders: Anterior chamber inflammation, Blepharitis, Corneal deposits, Corneal neovascularization, Eye discharge, Eye pruritus, Eyelid pain, Hyphema, Keratitis, Macular fibrosis, Posterior capsule opacification
- General disorders and administration site conditions: Disease progression
- Infections and infestations: Corneal abscess
- Investigations: Blood pressure increased
- Musculoskeletal and connective tissue disorders: Joint swelling
- Nervous system disorders: Headache, Paraesthesia

8.4 Post-Market Adverse Reactions

Because adverse events are spontaneously reported from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Eye pain was the main adverse event observed during the post-marketing period.

9 DRUG INTERACTIONS

9.1 Overview

9.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.3 Drug-Food Interactions

Interactions with food have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 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. Nerve growth factor receptors are expressed in the anterior segment of

the eye (cornea, conjunctiva, iris, ciliary body, and lens), by the lacrimal gland, and by posterior segment intraocular tissues. The treatment with cenegermin (a recombinant form of human nerve growth factor), administered as eye drops, is intended to restore the innervation of the corneal area affected in neurotrophic keratitis patients and to allow restoration of corneal integrity.

10.2 Pharmacodynamics

No pharmacodynamic studies have been conducted in humans with cenegermin (with or without methionine).

10.3 Pharmacokinetics

No pharmacokinetic studies have been conducted in humans with the commercial formulation of OXERVATE (cenegermin with methionine). The pharmacokinetic profile of cenegermin (without methionine) was assessed in healthy volunteers at ocular concentrations up to 180 mcg/mL. In patients where there was detectable systemic cenegermin, levels were similar to baseline.

Absorption: Cenegermin is primarily absorbed in the conjunctiva and peri-orbital tissue and to a minor extent through the cornea following ocular administration.

Distribution: After eye drop administration, cenegermin is distributed mainly in the anterior portion of the eye, although a study with radiolabelled cenegermin in rats at doses significantly higher than those administered by eye drops in humans to treat neurotrophic keratitis has shown that the drug also reaches the retina and other posterior parts of the eye. In addition, cenegermin was shown to drain through the nasolacrimal and nasopharyngeal ducts in rats and is expected to reach the oral cavity and gastrointestinal tract at low concentrations in humans.

Metabolism: Cenegermin is a protein and is expected to be degraded to small peptides and individual amino acids.

Elimination: Ocular administered cenegermin is mainly eliminated by tear secretion and the remainder biotransformed by local tissue proteases.

Special Populations and Conditions

Geriatrics: No pharmacokinetic studies have been conducted in humans with the commercial formulation of OXERVATE (cenegermin with methionine). Sample sizes were inadequate to assess any difference in the pharmacokinetics of cenegermin (without methionine) between younger and older adult patients.

Hepatic Insufficiency: There is no clinical information on the potential effects of hepatic impairment on the pharmacokinetics of cenegermin (with or without methionine).

Renal Insufficiency: There is no clinical information on the potential effects of renal impairment on the pharmacokinetics of cenegermin (with or without methionine).

11 STORAGE, STABILITY AND DISPOSAL

11.1 Storage at the Pharmacy

The weekly carton containing the 7 X 1 mL OXERVATE multi-dose vials must be stored in a freezer (-20 ±5 °C) until time of dispensing. The *Delivery System Kit* carton without the OXERVATE vials can be stored at room temperature.

11.2 Storage by the Patient

- The patient will receive a weekly carton including 7 vials of OXERVATE in the *Delivery System Kit* insulated pack. As soon as the patient is at home (and no later than 5 hours from when the patient receives OXERVATE at the pharmacy), the carton containing the 7 X 1 mL OXERVATE multi-dose vials is to be stored in the refrigerator (2°C to 8 °C) for up to 14 days. The *Delivery System Kit* carton without the OXERVATE vials can be stored at room temperature.

- The patient may thaw only the number of frozen OXERVATE vials required for use over the course of a single day at room temperature up to 25°C. Each vial can take approximately 30 minutes to thaw.

12 SPECIAL HANDLING INSTRUCTIONS

- An individual vial of OXERVATE (cenegermin) is to be removed from the refrigerator for use over the course of a single day. Once the vial adapter is connected to the vial, it is considered “open” and to be stored in the refrigerator (2°C to 8 °C) or below 25°C and must be used within 12 hours. To decrease the risk of introducing microbial contamination, it is important for patients to carefully follow the instructions for cleaning of hands and materials during handling, assembly, and storage of the vial, vial adapter, and pipettes. After 12 hours, the vial contents are to be discarded irrespective of whether some residual product remains in the vial.

- Do not refreeze the vial. Do not shake the vial.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	cenegermin
Molecular formula and molecular mass:	Molecular formula has been determined to be $C_{583}H_{908}N_{166}O_{173}S_{8.}$ Cenegermin monomer consists of 118 amino acids with a calculated weight of 13266 Daltons.
Structural formula:	Cenegermin is a recombinant human form of Nerve Growth Factor (rhNGF) produced by *Escherichia coli* (*E. coli*) bacteria into which has been inserted the DNA sequence of human proNGF. The protein has an amino acid sequence that is identical to human NGF, with the exception of two amino acids at the furin cleavage site, necessary for expression of homogeneous rhNGF during the process. The pro-sequence is further cleaved during the production process, thus the modifications have no influence on the final active ingredient which is identical to naturally secreted human protein.
Physiochemical properties:	Cenegermin drug substance is a clear, colorless solution with a pH of 7.0-7.4.

Product Characteristics

Cenegermin ophthalmic solution is a clear, colorless sterile preservative-free solution with a pH of 7.0-7.4 and osmolality 280-320 mOsm/kg.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 3: Summary of patient demographics for clinical trials in the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis

Study	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (%)
NGF0212	multicenter, randomized, double-blinded, vehicle-controlled	OXERVATE*: 0.001% (10 mcg/mL), 0.002% (20 mcg/mL); Vehicle Topical, Ocular; 8 week study with a 48 or 56 week follow-up period	174 patients with moderate or severe neurotrophic keratitis (OXERVATE**: 118; Vehicle: 56)	61 (18-95) years	M (40%) F (60%)
NGF0214	multicenter, randomized, double-blinded, vehicle-controlled	OXERVATE: 0.002% (20 mcg/mL); Vehicle Topical, Ocular; 8 week study with a 24 or 32 week follow-up period	48 patients with moderate or severe neurotrophic keratitis (OXERVATE: 24; Vehicle: 24)	65 (33-94) years	M (40%) F (60%)

* without the L-methionine non-medicinal ingredient
** Study NGF0212 – Phase I: OXERVATE n= 14, Vehicle n= 4; Phase II: OXERVATE n= 104, Vehicle n= 52
NK = neurotrophic keratitis

The efficacy and safety of OXERVATE were evaluated in two multicenter, randomized, double-blinded, vehicle-controlled clinical studies (NGF0212 and NGF0214) in adult patients with moderate (persistent epithelial defect) (PED) or severe (corneal ulcer) neurotrophic keratitis refractory to non-surgical treatments. In both studies, patients received OXERVATE or vehicle 6 times daily in the affected eye(s) for 8 weeks, and underwent a follow-up period. In Study NGF0212, only patients with monolateral disease could be enrolled, while in Study NGF0214 enrollment was allowed also for patients with bilateral disease.

Primary efficacy endpoint was the percentage of patients experiencing complete resolution of corneal staining, defined as no corneal fluorescein staining in the area of the PED or corneal ulcer and no persistent staining elsewhere in the cornea (i.e., 0 mm lesion size and no residual staining), as determined by a Central Reading Center, at the Week 4 and Week 8 visits.

The key secondary efficacy endpoint was the percentage of patients achieving corneal healing, defined as the greatest diameter of <0.5 mm of the corneal fluorescein staining in the area of the PED or corneal ulcer (i.e., <0.5 mm lesion size), as determined by a Central Reading Center, at the Week 4 and Week 8 visits.

In addition, the percentage of patients experiencing complete corneal clearing (grade 0 on the modified Oxford scale), the least squares mean change in best corrected distance visual acuity

score (Early Treatment Diabetic Retinopathy Study letters) from baseline, and improvement in corneal sensitivity as measured in millimeters by Cochet-Bonnet aesthesiometry (difference compared to baseline >0) were also measured after 8 weeks of treatment in both studies. Overall reduction in the corneal lesion size was also assessed by the Central Reading Center in both studies.

14.2 Study Results

Table 4 below summarizes the results of cenegermin versus vehicle treatment after 8 weeks of controlled treatment in the two clinical studies.

Table 4: Efficacy endpoints related to corneal healing after 8 weeks of controlled treatment in two randomized trials: ITT population

	NGF0212		NGF0214	
	OXERVATE* (N=52)	**Vehicle (N=52)**	**OXERVATE (N=24)**	**Vehicle (N=24)**
Completely stain-free (PED or corneal ulcer 0 mm staining; no other persistent staining) [NRI]:				
n (%)	34/52 (65.4%)	17/52 (32.7%)	14/24 (58.3%)	3/24 (12.5%)
Difference in % (95% CI)**	+32.7% (14.5, 50.9)		+45.8% (22.1, 69.6)	
P value***	<0.001		<0.001	
Completely healed (PED or corneal ulcer <0.5 mm staining) [NRI]:				
n (%)	35/52 (67.3%)	22/52 (42.3%)	15/24 (65.2%)	6/24 (25.0%)
Difference in % (95% CI)**	+25.0% (6.5, 43.5)		+37.5% (11.5, 63.5)	
P value***	0.010		0.009	
Change from baseline PED or corneal ulcer size [observed case]:				
Mean % change from baseline	-85.4%	-32.6%	-88.6%	-15.7%
LS mean difference	-52.8%		-72.9%	

* Without the L-methionine non-medicinal ingredient
**Two-sample test of proportions
***2x2 Chi-square
NRI: non-responder imputation. Worst-case analysis; patients with missing data for any reason were considered as failure.
CI.: confidence interval
n: number of patients achieving endpoint, N=total number of patients in group.

In both trials, the percentage of patients who achieved complete corneal clearing (defined as a modified Oxford score of zero) at Week 8 was numerically higher in the OXERVATE treatment group than in the vehicle control group. Numerical improvements in BCDVA and corneal sensitivity were also observed in OXERVATE-treated patients as compared to vehicle at Week 8.

In both trials, vehicle-treated patients that were not completely healed at Week 8 were re-randomized to receive OXERVATE. Efficacy results after 8 weeks of OXERVATE treatment in these patients were similar to those observed in patients treated with OXERVATE in the

controlled treatment period.

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.

15 NON-CLINICAL TOXICOLOGY

15.1 Safety Pharmacology

A modified Irwin safety pharmacology study was conducted in Wistar rats administered up to 0.25 mg/kg/day rhNGF topically (eye drops) over four weeks. No rhNGF-related adverse effects on the central nervous system were observed.

15.2 General Toxicology

Ocular toxicity of rhNGF was evaluated in repeat-dose studies conducted in healthy Wistar rats (26-week study; 5 µL/eye TID) and New Zealand White rabbits (2-month study; 30 µL/eye TID) dosed by the topical ocular route of administration (eye drops). In these studies, the ocular NOAELs were the highest doses of rhNGF tested, 18 mcg/eye/day in rats and 108 mcg/eye/day in rabbits. These NOAELs corresponded to an ocular safety margin of 3.8- and 23-fold the maximum recommended human ophthalmic dose (MRHOD) in rats and rabbits, respectively, as calculated by direct comparison of the animal dose to the human dose.

Systemic toxicity was evaluated in repeat-dose studies conducted in rats and rabbits, using the topical ocular (eye drop) and subcutaneous routes of administration. The ocular studies consisted of a 26-week study conducted in Wistar rats at doses of 120, 160, and 240 mcg/kg/day and a 2-month study conducted in New Zealand White rabbits at doses of 19 and 37 mcg/kg/day. The subcutaneous studies consisted of a 26-week study conducted in Wistar rats at doses of 333 and 667 mcg/kg/day and a 3-month study conducted in New Zealand White rabbits at doses of 56 and 111 mcg/kg/day. The main findings consisted of adverse ovarian effects (i.e. increased ovary weights, cell proliferation, hemorrhagic cysts, and corpora lutea), which were observed in both rats and rabbits following topical ocular administration and in rabbits following subcutaneous administration. Similar effects were not observed in the subcutaneous rat study. A drug-related effect could not be ruled out for the ovarian findings. Immune reactions (including swelling and erythema of the head, ears, tail, and/or legs) were also observed in animals across multiple studies; however, these immune reactions were likely due to rhNGF's nature as a heterologous protein in animals, and thus, the effect is unlikely to be relevant to humans. No other rhNGF-related adverse effects were observed in these studies. Thus, the NOAEL for the systemic toxicity of rhNGF in male animals was the highest dose tested in each study, while NOAELs for female animals were based on the adverse ovarian effects observed when applicable. Specifically, in the ocular rat study, the NOAELs in males and females were determined to be 240 and 160 mcg/kg/day, respectively, corresponding to safety margins of 249- and 166-fold the MRHOD. In the ocular rabbit study, the NOAEL in males and females was 37 mcg/kg, corresponding to a safety margin of 77-fold the MRHOD. In the subcutaneous rat study, the NOAEL in both males and females was 667 mcg/kg, the highest dose tested, corresponding to a safety margin of 693-fold the MRHOD. In the subcutaneous rabbit study, the NOAELs in males and females were 111 and 56 mcg/kg, respectively, corresponding to safety margins of 231- and 116-fold the MRHOD. Systemic safety margins were calculated based on doses expressed on a body surface area basis.

15.3 Carcinogenicity

No studies have been performed to evaluate the carcinogenic potential of cenegermin.

15.4 Genotoxicity

No studies have been performed to evaluate the genotoxic potential of cenegermin.

15.5 Reproductive and Developmental Toxicology

A combined fertility and embryo fetal development study was conducted in Wistar rats at doses of 133 and 267 mcg/kg/day administered by subcutaneous injection once daily to males for 42 to 43 days (starting from 2 weeks pre-mating, during mating, and post-mating until the day prior to scheduled necropsy) and in females for 33 to 46 days (starting from 2 weeks pre-mating, during pairing, and during gestation until gestation day [GD] 17). No rhNGF-related adverse effects on fertility were noted. However, there was an increase in the incidence of fetal malformations (i.e. hydrocephaly and ureter abnormalities [convoluted and/or dilated]) in the high-dose group and an increase in the rate of post-implantation loss in both rhNGF groups. Thus, a NOAEL for the developmental toxicity of rhNGF in rats could not be established in this study.

An embryo fetal development study was conducted in pregnant New Zealand White rabbits at doses of 42 and 83 mcg/kg/day administered by subcutaneous injection once daily from GD 7 to 20. An increase in the incidence of fetal cardiac malformations (i.e. ventricular and atrial septal defects, enlarged heart, and aortic arch dilation) were observed in the high-dose group and an increase in the rate of post-implantation loss was observed in both rhNGF groups. Thus, as in rats, a NOAEL for the developmental toxicity of rhNGF in rabbits could not be established.

A pre- and post-natal development toxicity study was also conducted in pregnant Wistar rats at doses of 133 and 267 mcg/kg/day administered by subcutaneous injection from GD 6 to post-natal day 21 to 23. No rhNGF-related adverse effects on development were observed in this study. The NOAEL was therefore determined to be 267 mcg/kg/day, the highest dose tested.

Since human systemic exposure to rhNGF following ocular administration at the MRHOD is expected to be low, the applicability of the animal developmental findings, which were observed following subcutaneous administration, to the reproductive and developmental risks of OXERVATE use in humans is unclear.

Consistent with the general toxicology studies, immune reactions were noted in the parental animals administered rhNGF in the above reproductive and developmental toxicity studies.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrOXERVATE™ (ox'-er-vayt)
(cenegermin ophthalmic solution, 0.002% [20 mcg/mL])

Read this carefully before you start taking **OXERVATE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **OXERVATE**.

What is OXERVATE used for?
OXERVATE is used to treat adults with moderate or severe 'neurotrophic keratitis'. This disease affects the cornea (the transparent layer in the front part of the eye) and causes defects. These defects will not heal on their own. They may get worse and turn into corneal ulcers. OXERVATE helps the cornea heal.

How does OXERVATE work?
OXERVATE contains a protein that helps your eye(s) heal and repair damage to the eye's surface.

What are the ingredients in OXERVATE?
Medicinal ingredients: cenegermin.
Non-medicinal ingredients: disodium hydrogen phosphate anhydrous, hydrochloric acid, mannitol, nitrogen, polyethylene glycol 6000, L-methionine, sodium dihydrogen phosphate dihydrate, hydroxypropylmethyl cellulose, sodium hydroxide, trehalose dehydrate, and water for injections.

OXERVATE comes in the following dosage forms:
Ophthalmic solution (eye drops), 0.002% (20 mcg/mL)

Do not use OXERVATE if:
- you are allergic to this drug or any of the ingredients.
- you are below 18 years of age.
- you are taking any eye drops containing corticosteroids (e.g. to treat ocular inflammation) or preservatives (e.g. benzalkonium chloride, polyquaternium-1, benzododecinium bromide, cetrimide). Eye drops containing these substances could slow down or interfere with the healing of your eye and should therefore be avoided during treatment with this medicine.
- you have an eye infection. The infection should be treated first. If you get an eye infection while using OXERVATE, you should stop your treatment and see your doctor right away.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OXERVATE. Talk about any health conditions or problems you may have, including if you:
- need surgery on your eye(s). You should not use this medicine if you need surgery or there are other problems with your eye(s).
- experience a severe eye reaction. Treatment with OXERVATE may cause you mild to moderate discomfort such as eye pain.
- have contact lenses. Contact lenses could interfere with the correct use of this medicine.

Remove them before using this medicine. **Wait 15 minutes after** using this medicine and then reinsert them.

Other warnings you should know about:
Tell your doctor:
- if you are pregnant or plan to become pregnant. It is not known if OXERVATE will harm your unborn baby.
- if you are breast-feeding. It is not known if this medicine passes into breast milk.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

You should wait **at least 15 minutes before or after** using OXERVATE if you use any other eye drops. This will help to avoid one eye drop diluting the other eye drop. If you also use an eye ointment or gel or an eye drop with a thick consistency, you should use OXERVATE **first**, and then wait **at least 15 minutes before** using the other medicine.

How to take OXERVATE:
You will receive an insulated container containing a weekly carton of OXERVATE. A separate delivery system carton will be provided. This will have medical devices for applying the medicine to your eye.

The weekly carton contains 7 vials of OXERVATE, 1 vial per day of the week.
Each vial contains enough medication to administer six doses. The separate delivery system carton contains 7 vial adapters, 42 pipettes, 42 disinfectant wipes and a card to record the dose. The carton includes spare adapter (1), pipettes (3), and wipes (3).

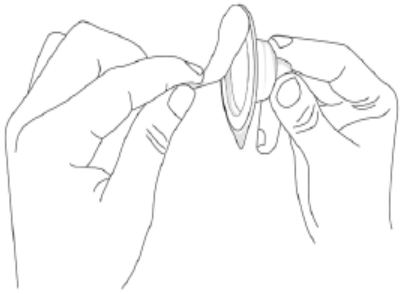
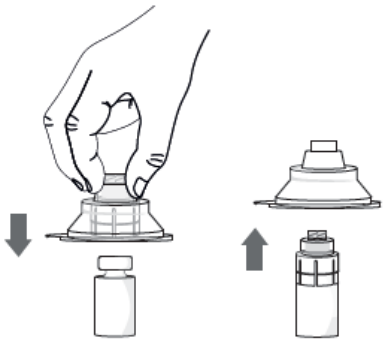
Remove the weekly carton of OXERVATE from the insulated container. Store OXERVATE in a fridge as soon as you can and no later than 5 hours from when you receive the medicine from your pharmacist. This medicine is stored in a freezer at the pharmacy. You will have to wait up to 30 minutes for the first vial to thaw before you start using it.

Follow Steps 1 to 19 each day you use OXERVATE:

Take one vial of this medicine from the fridge in the morning. Take at the same time each morning and prepare it in the following way:

Step 1. Wash your hands.

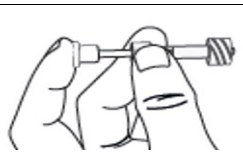
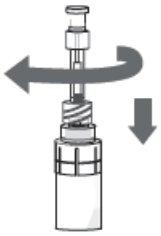
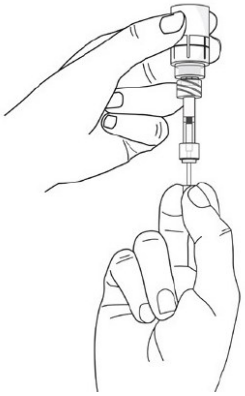
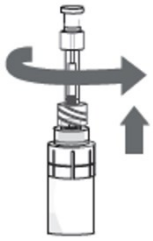
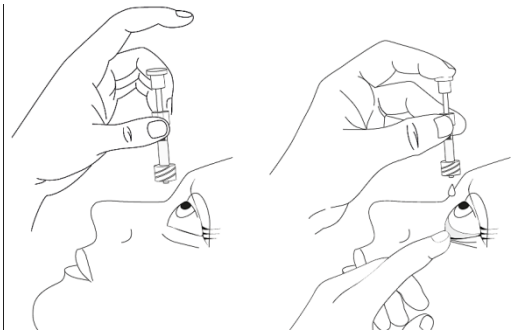
Step 2. If you wear contact lenses, take them out before using the drops.

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. Once the vial adapter has been connected correctly, it should not be removed from the vial. **Step 6.** Remove and discard 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). The vial should be stored in the fridge between doses. If needed, the vial can be stored at room temperature below 25 ºC. Do not remove the vial adapter between doses.

To withdraw and administer each dose of this medicine, follow the steps below:

Step 7. Take a single disinfectant wipe and gently clean the surface of the valve on the connector part of the vial adapter. After cleaning, wait for approximately 1 minute to allow the valve to dry.	

Step 8. Take a pipette (dropper), by removing it from its protective packaging.	
Step 9. Screw the pipette (clockwise) into the connector part of the vial adapter. **Step 10.** Ensure that the pipette plunger is pushed all the way down.	
Step 11. Turn the vial upside-down (with the pipette still connected) and gently pull the plunger until it stops, to draw the solution into the pipette. Ensure the plunger has reached the stop point. **Step 12.** Check the pipette to ensure it contains the eye drops solution. Air bubbles may cause blockage and prevent the pipette from filling properly (especially at first withdrawal). 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. Once it has been correctly filled, unscrew the pipette from the connector part of the vial adapter.	
Step 14. • Holding the pipette, pointing down, between your middle finger and thumb, tilt your head back and position the pipette above your affected eye. • Pull down your lower eyelid, folding between the inner eyelid and the eyeball. • Gently push the plunger in until a single drop is dropped into the folding tissue. 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.	

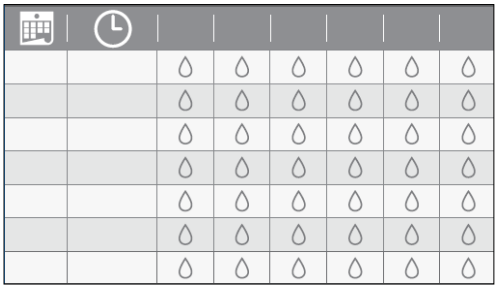
Step 15. Immediately discard the used pipette after use, even if there is still some liquid left in it.

If a drop misses your eye, try again, using a new pipette and wipe.

Step 16. After each use throughout the day, place the vial back in the fridge (or keep it below 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 six times a day, using a new disinfectant wipe and a new pipette each time. Be sure to always wash your hands before you handle the vial or pipettes.

If you use drops in both eyes, repeat the above instructions for your other eye using a new pipette (in this case, you will need to use 2 vials per day).

Step 18. Discard the used vial at the end of each day (even if there is still some liquid left in it), and in any case no later than 12 hours from the time you connected the vial adapter to it.	
Step 19. Track each time you use an eye drop of this medicine on the weekly dose recording card provided with the delivery system. This will allow you to control that six doses have been taken at the end of each treatment day. On this card you should also write down the date of the first use of the weekly supply and the time of the vial opening (i.e. when you connect the vial adapter to the vial) over the week.	

To ensure accurate dosing every 2 hours, you could set an alarm as a reminder for dosing.

Usual dose:
The recommended dose is 1 drop in the affected eye 6 times a day at 2-hourly intervals, starting in the morning (i.e. 6 drops per day within 12 hours). You should continue your treatment for 8 weeks**.**

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure**.**

Your vision may be temporarily blurred immediately after using this medicine. If this happens, **wait until your vision clears before you drive or use machines**.
Do not take other eye medicines without talking to your doctor.

Overdose:
If you use more than you should, flush the affected eye with lukewarm water. Do not put in any more drops until it is time for your next regular dose. Continue with your next dose as scheduled.

If you think you have taken too much OXERVATE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to use OXERVATE, continue with your next dose as scheduled. Do not use a double dose to make up for the forgotten dose. You can give the missed dose 2 hours after your last scheduled dose of the day, provided this is still within 12 hours from first opening the daily vial. Do not use more than 6 drops each day in the affected eye(s).

Speak to your doctor first if you intend to stop using OXERVATE.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

What are possible side effects from using OXERVATE?
These are not all the possible side effects you may feel when taking OXERVATE. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effect of OXERVATE is eye pain. Other common side effects may include pain in the eyelid, feeling that there is something in the eye, increase of tears (this could include symptoms such as discharge in the eye), infection of the cornea with pus and swelling, and inflammation of the eye.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting; https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store the weekly carton containing 7 vials of OXERVATE in the fridge 2-8°C.

After the vial adapter is connected to the vial, OXERVATE can be stored in the fridge or below 25°C. Discard the used vial at the end of the day (even if there is still some liquid left in it), and in any case no later than 12 hours from the time you connected the vial adapter to it.

Do not use this medicine after the expiry date which is stated on the OXERVATE outer carton and vial label.

The pipettes included in the delivery system are single-use only. Each pipette should be discarded immediately after using, even if there is still some liquid left in it.

Keep out of reach and sight of children.

If you want more information about OXERVATE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html) or by calling 1-800-<phone number>.

This leaflet was prepared by Dompé farmaceutici S.p.A.

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