The format of this leaflet was determined by the Ministry of Health and its content was checked and approved *in January 2019*

Oxervate

1. NAME OF THE MEDICINAL PRODUCT

OXERVATE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 20 micrograms of cenegermin*.

* Recombinant form of human nerve growth factor produced in *Escherichia Coli*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution (eye drops).
Clear, colourless solution. pH 7.0-7.4 and osmolarity 280-320 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults.

4.2 Posology and method of administration

Treatment should be initiated and supervised by an ophthalmologist or a healthcare professional qualified in ophthalmology.

Posology

Adults:
The recommended dose is one drop of OXERVATE in the conjunctival sac of the affected eye(s), 6 times a day at 2 hourly intervals, starting from the morning and within 12 hours. Treatment should be continued for eight weeks.

Patients with an eye infection should be treated before starting therapy with OXERVATE (see section 4.4).

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 instil more than one drop in the affected eye(s) during any administration.

Special populations
Elderly:
No dose adjustment is required in patients 65 years of age and older.

Hepatic and renal impairment:

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

Paediatric population:
The safety and efficacy of this medicinal product in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration

For ocular use only.

Precautions to be taken before administering the medicinal product:

Patients should be instructed to wash their hands before use.

OXERVATE should only be administered using the associated delivery system (vial adapter and pipettes), according to the instructions presented in section 6.6.
An individual pipette should be used per application.

If more than one topical ophthalmic product is being used, the eye drops must be administered at least 15 minutes apart, to avoid diluting the other product. If eye ointment, gel or other viscous eye drops are used, they should be administered 15 minutes following OXERVATE treatment (see also section 4.5).

In case of concomitant use with contact lenses, see section 4.4.
For instructions on preparation and handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 as cenegermin should not be used in patients requiring immediate surgery.

Eye reactions

OXERVATE may cause mild to moderate eye discomfort, such as eye pain, to the patient. The patient should be advised to contact the 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 (see section 4.5).

Eye infections

An eye infection should be treated before use of OXERVATE. Should an eye infection occur, OXERVATE should be suspended until infection resolution (see section 4.2).

Ocular cancer

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

Contact lenses

Patients should be instructed to remove contact lenses before applying OXERVATE and to wait 15 minutes after instillation of the dose before reinsertion, 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.

4.5 Interaction with other medicinal products and other forms of interaction

Other topical ophthalmic products may be used during treatment with OXERVATE when used 15 minutes apart, with the exception of agents known to inhibit epithelial healing (e.g. corticosteroids or eye drops containing preservatives such as benzalkonium chloride, polyquaternium-1, benzododecinium bromide, cetrimide and other quaternary ammonium derivatives) (see sections 4.2 and 4.4). If eye ointment, gel or other viscous eye drops are used, OXERVATE should be administered first.

No interaction studies with other medicinal products have been performed.
As systemic absorption of cenegermin after use of the medicinal product is negligible or not detectable, no drug interactions are anticipated.

4.6 Fertility, pregnancy, and lactation

Pregnancy

There are no data from the use of cenegermin in pregnant women. Animal studies with cenegermin do not indicate direct or indirect harmful effects with respect to reproductive toxicity when administered subcutaneously (see section 5.3).

Systemic exposure to cenegermin is negligible or does not occur.

As a precautionary measure, it is preferable to avoid the use of OXERVATE during pregnancy.

Breastfeeding

It is not known whether cenegermin is excreted in human milk.

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from this therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of cenegermin on human fertility.

4.7 Effects on ability to drive and use machines

The treatment has minor influence on the ability to drive and use machines, as it may cause temporary blurred vision or other visual disturbances, which is expected to last a few minutes after instillation. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients suffering from neurotrophic keratitis and treated with OXERVATE during clinical studies include eye pain (11.1 %), eye inflammation (8.3 %), which may include anterior chamber inflammation and hyphaema; lacrimation increased (5.6 %), with symptoms such as eye discharge; eyelid pain (5.6 %) and foreign body sensation in the eye (5.6 %).

Eye pain was the most frequently reported adverse reaction, followed by eye irritation and abnormal sensation in the eye, when considering the whole population treated with the medicinal product (i.e. population included in clinical trials also on indications other than neurotrophic keratitis).

Tabulated list of adverse reactions

The following adverse reactions listed below were observed in clinical studies in patients suffering from neurotrophic keratitis, treated with OXERVATE 20 µg/ml.

Adverse drug reactions are presented below according to MedDRA system organ classification (SOC and Preferred Term Level).
They are ranked according to system organ class and classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Corneal abscess
Nervous system disorders	Common	Headache
Eye disorders	Very common	Eye pain
	Common	Eye inflammation, eyelid pain, foreign body sensation in the eye, lacrimation increased, blepharitis, conjunctival hyperaemia, photophobia, eye irritation
	Uncommon	Corneal neovascularization

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by an online form:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).
Additionally, suspected adverse reactions can be reported to drugsafety@mind-farma.com.

4.9 Overdose

A topical overdose is not likely to occur or to be associated with toxicity. A topical overdose of cenegermin may be flushed from the eye(s) with lukewarm water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: cenegermin (recombinant human nerve growth factor),
ATC code: S01XA24.

Mechanism of action

OXERVATE contains cenegermin, a recombinant form of human nerve growth factor.

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, administered as eye drops, is intended to allow restoration of corneal integrity.

Clinical efficacy and safety

The efficacy and safety of OXERVATE were evaluated in two multicentre, randomised, double-masked, vehicle-controlled clinical studies (NGF0212 and NGF0214) in patients with moderate (persisted epithelial defect) or severe (corneal ulcer) neurotropic 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.

Study NGF0214 enrolled 48 patients (mean age 65±14 years, range 33-94 years) treated with OXERVATE 20 µg/ml or vehicle (24 patients per arm). Study NGF0212 enrolled a total of 174 patients (mean age 61±16 years, range 18-95 years), who have been exposed to OXERVATE and vehicle without the L-methionine excipient; 156 patients were assessed independently for efficacy, comparing two different dosages of the medicinal product with 20 and 10 µg/ml cenegermin to vehicle (52 patients per arm).
The table below summarizes the results for complete corneal healing of the persistent epithelial defect or corneal ulcer (the primary endpoint, defined as the greatest diameter of corneal fluorescein staining <0.5 mm) after 4 and 8 weeks of treatment for patients who received OXERVATE 20 µg/ml or vehicle in the two studies.

		Study NGF0214		**Study NGF0212**	
Results after 4 and 8 weeks of treatment		**Week 4**	**Week 8**	**Week 4**	**Week 8**
Complete corneal healing rate	OXERVATE	56.5 %	69.6 %	58.0 %	74.0 %
	vehicle	37.5 %	29.2 %	19.6 %	43.1 %
	(p value)	(0.191)	(0.006)	(0.001)	(0.002)

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 any improvement in corneal sensitivity as measured in millimetres by Cochet-Bonnet aesthesiometry (difference compared to baseline >0) was also measured after 8 weeks of treatment in both studies, and summarized in the table below.

Results after 8 weeks of treatment		**Study NGF0214**	**Study NGF0212**
Complete corneal clearing	OXERVATE	22.7 %	21.4 %
	Vehicle	4.2 %	10.0 %
	(p value)	(0.062)	(0.157)
Best corrected distance visual acuity	OXERVATE	6.11	11.9
	Vehicle	3.53	6.9
	(p value)	(0.143)	(0.213)
Corneal sensitivity inside lesion	OXERVATE	72.2 %	76.3 %
	Vehicle	60.0 %	68.4 %
	(p value)	(0.458)	(0.442)

Patients considered completely healed at the end of 8 weeks of treatment with OXERVATE did not tend to have recurrences within the 12 months follow-up period of study NGF0212. Specifically, more than 80 %

of the 31 patients who were healed after initial OXERVATE 20 µg/ml treatment and for whom a response was available, remained completely healed at the end of the 12 months follow up period.

5.2 Pharmacokinetic properties

Absorption

Cenegermin is mostly removed from the eye with the tear production and through the naso-lacrimal duct; the minor portion that is absorbed occurs mostly in the conjunctiva and peri-orbital tissue and to a minor extent through the cornea following ocular administration.
Pharmacokinetic profiling of patients included in studies found no accumulation effect of cenegermin. In general, the systemic absorption of OXERVATE is negligible.

Distribution

After eye drop administration, cenegermin is distributed particularly in the anterior portion of the eye, although a study with radiolabelled cenegermin in rats has shown that it also reaches the retina and other posterior parts of the eye at doses significantly higher than those administered by eye drops in humans to treat neurotrophic keratitis. At the ocular doses, cenegermin is not distributed throughout body tissues as there is no systemic absorption above the natural baseline levels.

Biotransformation

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

Elimination

Cenegermin administered by eye drops is mostly eliminated with the tear secretion.

5.3 Preclinical safety data

Nonclinical data reveal no hazard for humans based on conventional studies of safety pharmacology (central nervous system), single-dose toxicity, repeat-dose toxicity and toxicity to reproduction, embryo-foetal development, pre- and post-natal development using ocular (eye drop), intravenous, and/or subcutaneous administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Trehalose dihydrate
Mannitol
Disodium hydrogen phosphate, anhydrous
Sodium dihydrogen phosphate, dihydrate
Hypromellose
Macrogol 6000
L-Methionine
Water for injections
Hydrochloric acid
Sodium hydroxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Opened vial
Once opened, the product must be stored below 25 °C or in the refrigerator (2- 8 °C) and used within 12 hours.

6.4 Special precautions for storage

OXERVATE vials
Pharmacy:
The weekly carton containing the vials must be stored in a freezer (-20 °C ±5 °C) for up to 24 months
Patient:
The patient will receive a weekly carton including 7 vials of OXERVATE in an insulated pack. As soon as the patient is at home (and no later than 5 hours from when the patient receives the product at the pharmacy), the weekly carton should be placed into the refrigerator, at 2-8 °C for maximum 7 daysIt should be noted that the frozen medicinal product received from the pharmacy could need up to 30 minutes for thawing.

An individual multi-dose vial of OXERVATE is to be removed from the refrigerator for use. Each opened vial can be stored in the refrigerator (2-8 °C) or below 25 °C, and used within 12 hours.
After this period of time the vial contents should be discarded irrespective of whether some residual product remains in the vial.

6.5 Nature and contents of container

1 ml OXERVATE solution in sterile, preservative-free multi-dose siliconized Type I glass vials, closed with a rubber stopper and an aluminium overseal with a polypropylene flip-off cap, presented in cardboard cartons.

Pack size: 7 multi-dose vials per carton

The patient will receive a weekly carton containing 7 vials of OXERVATE.

This medicinal product should only be used with specific vial adapters and disposable devices (pipettes) that will be provided separately from the weekly OXERVATE carton.
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 will be provided separately, together with a dose recording card. Extra adapter (1), pipettes (3) and wipes (3) will also be provided as spares.

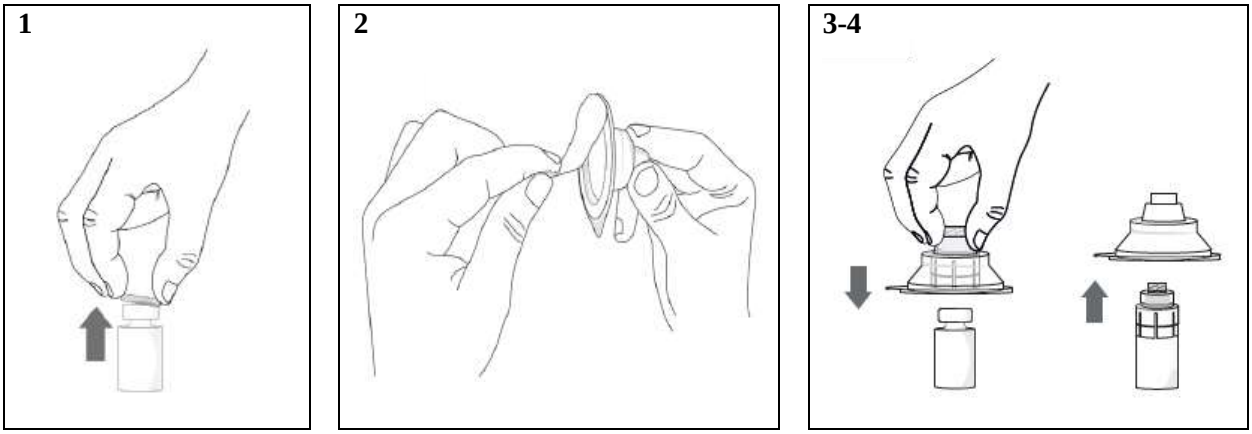
6.6 Special precautions for disposal and other handling

The patient will receive a weekly carton containing 7 multi-dose vials of OXERVATE, which should be stored in a refrigerator until the day of use.

The patient will also receive separately vial adapters, pipettes and disinfectant wipes.

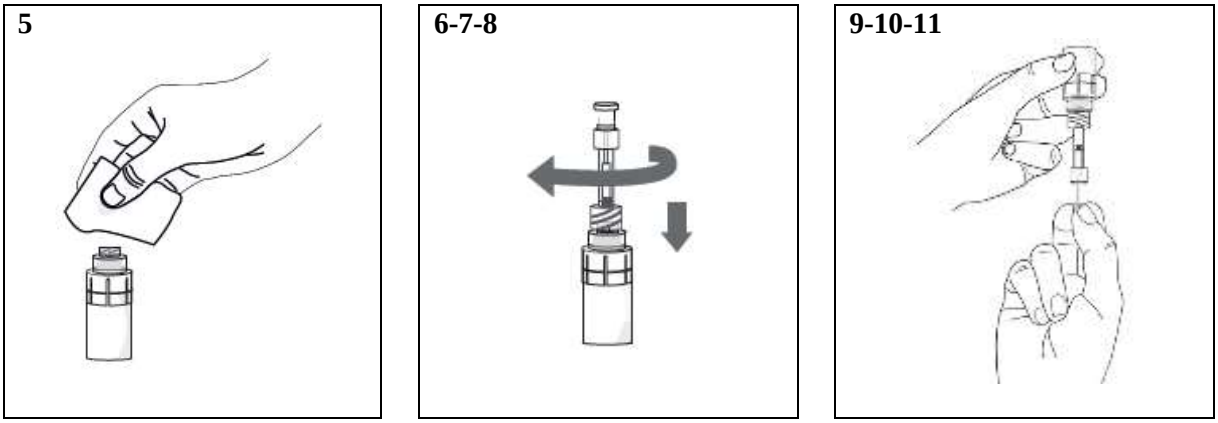
An individual multi-dose vial of OXERVATE should be taken from the refrigerator at the same time each morning bearing in mind the 12 hour treatment schedule. The multi-dose vial containing the product should be prepared according to the following instructions:

1) With clean freshly-washed hands, place the vial on a steady flat surface and remove the plastic flip-off cap.
2) Peel-off the back of the vial adapter blister pack.
3) Without removing the vial adapter from its blister pack, connect the vial adapter to the vial by firmly pushing the vial adapter down vertically until it snaps into place over the neck of the vial and the spike of the vial adapter pierces through the vial's rubber stopper. Once the vial adapter has been connected correctly, it should not be removed from the vial.
4) Remove and discard the vial adapter blister pack. Avoid touching the surface of the adapter.



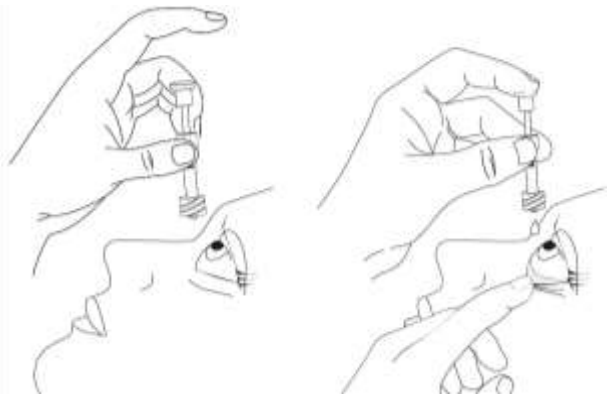
To withdraw and administer each dose of OXERVATE solution, the steps below should be followed:

5) Take an individual disinfectant wipe and gently clean the surface of the valve on the luer lock connector of the vial adapter. After cleaning, the valve should be allowed to dry for approximately one minute.
6) Take a pipette and remove it from the protective packaging.
7) Screw the pipette clockwise into the luer lock connector of the vial adapter.
8) Ensure that the pipette plunger is pushed all the way down.
9) Turn the vial upside-down with the pipette connected and gently pull the pipette plunger outwards until it stops, to draw the solution into the pipette (ensure that the plunger has reached the stop point).
10) Check the pipette and confirm that it contains some of the 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.
11) Once it has been correctly filled, unscrew the pipette from the luer lock connector of the vial adapter.



12) Hold the pipette, pointing down, between the middle finger and thumb, tilt the head back and position the pipette above the affected eye. Pull down the lower eyelid. Gently push the pipette plunger in until a single drop is instilled into the conjunctival fornix.
13) Immediately discard the used pipette and wipe after instillation.
14) If a mistake is made and a drop is not instilled into the eye, repeat the steps described above using a new pipette and wipe.
15) Throughout the day, the vial can either be placed back in the fridge after each use or stored below 25 °C (with the vial adapter still connected).

12-13-14



The administration instructions above (steps 5 to 15) should be repeated every 2 hours (six times per day) using a new disinfectant wipe and a new pipette each time.

The vial and any remaining solution must be discarded at the end of the day, and no later than 12 hours from the time the vial adapter was connected (irrespective of whether any residual solution remains in the vial).

To ensure accurate dosing every 2 hours, the patient should be advised to set an alarm as a reminder for dosing.

To control that six doses have been taken every day, the patient should be advised to use the weekly dose recording card provided with the delivery system. On that card the patient should track the date of the first use of the weekly supply, the time of the vial opening (i.e. when the vial adapter is connected to the vial), and the time of daily ocular instillations occurring over the week.

A new OXERVATE supply will be issued each week for the duration of the treatment period.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER:

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

8. MARKETING AUTHORISATION HOLDER

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This leaflet dormat has been determined by the Ministry of Health and the content has been checked and approved in January 2019