Drug Coverage Policy

Effective Date.....11/1/2025
Coverage Policy Number IP0302
Policy Title.....Oxervate

Ophthalmology – Oxervate

- Oxervate™ (cenegermin-bkbj ophthalmic solution – Dompé)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Oxervate, a recombinant human nerve growth factor, is indicated for the treatment of **neurotrophic keratitis**.[1]

Safety and effectiveness of Oxervate have been established in the pediatric population.[1] Use in children is supported from evidence from adequate and well-controlled trials of Oxervate in adults and additional safety data in pediatric patients ≥ 2 years of age.

Oxervate is supplied in cartons; each carton contains seven multi-dose vials.[1] Each vial contains enough medication to treat one eye per day; patients who are treating both eyes require two vials per day.

Duration of Treatment
The recommended dosing regimen for one course of treatment is one drop six times a day (at 2 hour intervals) for 8 weeks.[1] In the NGF0214 study, recurrence after receipt of 8 weeks of therapy occurred in six patients; five of these patients underwent retreatment with a second 8-week course of Oxervate.[2] Two patients experienced recurrence during the double-masked treatment period: one patient underwent retreatment on the day after completing the masked treatment period and one patient under retreatment 39 days after the last visit of the masked treatment period. During the open-label treatment period, where all of the patients who were randomized to vehicle during the double-masked study received Oxervate), three patients with recurrence were retreated; retreatment was initiated between 7 days and 37 days after the last visit of the open-label treatment period. .[2] Four of these patients achieved corneal healing after retreatment, which was maintained through the end of the follow-up period. There are no data to support use of Oxervate beyond 16 weeks (two 8-week treatment courses).

Disease Overview
Neurotrophic keratitis, a rare degenerative disease, is characterized by corneal epithelium breakdown, impairment of corneal healing, and development of corneal ulceration, melting, and perforation.[3-6,9] Corneal epithelial cells release various neurotrophic growth factors, including nerve growth factors, which are important in maintaining the integrity and function of the ocular surface and in stimulating both epithelial and nerve fiber proliferation and survival.[7,8] When corneal sensory innervation is impaired, reduction of both protective reflexes and trophic neuromodulators essential for the vitality, metabolism, and wound healing of the ocular surface tissues results. *In vivo* studies have shown that increasing nerve growth factor concentration after injury can accelerate healing.[4,8]

Guidelines/Recommendations
Neurotrophic keratosis is classified into three stages: Stage 1 (mild), corneal epithelial changes; Stage 2 (moderate), corneal epithelial defect; Stage 3 (severe), corneal ulcer, perforation, melting.[6] Prior to the approval of Oxervate, there were no approved pharmacologic therapies for the treatment of neurotrophic keratitis.[3] If neurotrophic keratitis is left untreated, the condition can progress to anatomical loss of the eye; even with treatment, loss of vision is common.[6,7] Treatment should target corneal sensory innervation impairment to restore corneal integrity; treatment goals are to stop progression and promote epithelial healing.

There are no formal clinical guidelines, although there are expert opinion on the diagnosis and treatment of neurotrophic keratitis.[6] Optimal care requires identifying and treating the underlying causes of neurotrophic keratitis; for example, using antiviral medications for herpetic disease, correcting eyelid abnormalities, controlling hemoglobin A1c levels in patients with diabetes, and providing supportive therapy for limbal stem cell deficiency. For all stages, optimal care includes discontinuation of all preservative-containing ophthalmic medications to the extent possible and use of preservative-free tear substitutes or lubricants is recommended. For patients with Stage 2 disease, Oxervate, prophylactic ophthalmic preservative-free antibiotics, oral tetracyclines (e.g., doxycycline), corneal therapeutic contact lenses, and fresh-frozen self-retained amniotic membrane may be considered. For patients with Stage 3 disease, all of the listed options for

Stage 2 disease as well as synthetic tissue adhesive, tarsorrhaphy, amniotic membrane transplant, and corneal neurotization are optimal treatments.

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for benefit coverage of Oxervate. All approvals are provided for the duration noted below. For initial treatment of neurotrophic keratitis, 8 weeks of treatment of Oxervate is approved (per affected eye[s]); for recurrence of neurotrophic keratitis, another 8 weeks of treatment can be approved. A total of 16 weeks (two 8-week treatment courses) per lifetime of Oxervate can be approved for treatment of initial and recurrent neurotrophic keratitis. Because of the specialized skills required for evaluation and diagnosis of patients treated with Oxervate as well as the monitoring required for adverse events and long-term efficacy, approval requires Oxervate to be prescribed by a physician who specializes in the condition being treated.

Oxervate is considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. **Neurotrophic Keratitis.** Approve if the patient meets ONE of the following (A or B):
   Note: The initial course is 8 weeks of treatment with Oxervate in the affected eye. If the patient has not yet received a total of 8 weeks of treatment in the affected eye, review under Initial Therapy. If the patient has already received at least 8 weeks of treatment in the affected eye, review under Patient Who Has Previously Received Oxervate .
   A) Initial Therapy. Approve up to 8 weeks per affected eye(s) if the patient meets BOTH of the following (i and ii):
   Note: If the patient has started treatment but did not receive 8 weeks, approve enough Oxervate to complete 8 weeks of treatment.
   i. Patient has received < 8 weeks of treatment in the affected eye(s); AND
   Note. Each course of Oxervate for the treatment of initial neurotrophic keratitis is 8 weeks (per affected eye[s]).
   ii. The medication is prescribed by an ophthalmologist or optometrist; OR
   B) Patient Who Has Previously Received Oxervate. Approve up to 8 weeks per affected eye(s) if the patient meets ALL of the following (i, ii, and iii):
   Note: If the patient has started treatment of recurrent neurotrophic keratisis, but did not receive 8 weeks, approve enough Oxervate to complete 8 weeks of treatment.
   i. Patient has received <16 weeks (total) of treatment in the affected eye(s) [per lifetime]; AND
   Note: Each course of Oxervate for the treatment of recurrent neurotrophic keratitis is 8 weeks (per affected eye[s]); a total of two 8-week treatment courses for initial and recurrent neurotrophic keratitis (per affected eye[s] per lifetime).
   ii. Patient has a recurrence of neurotrophic keratitis; AND
   iii. The medication is prescribed by an ophthalmologist or optometrist.

Conditions Not Covered

Oxervate for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Treatment Duration of > 16 Weeks Total Per Affected Eye(s) Per Lifetime.** Available data supports use of Oxervate for 8 weeks for initial treatment of neurotrophic keratitis and an additional 8 weeks for treatment of recurrent neurotrophic keratitis (16 weeks total) per affected eye(s). [2,7] There are no data to support use of Oxervate beyond two 8-week treatment courses.

References

1. Oxervate™ ophthalmic solution [prescribing information]. San Mateo: Dompé; December 2024.
2. Pflugfelder SC, Massaro-Giordano M, Perez VL, et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy. A multicenter randomized vehicle-controlled pivotal trial. *Ophthalmology*. 2020;127:127:14-26.
3. Oxervate. FDA Clinical Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761094Orig1s000TOC.cfm. Accessed on July 10, 2025.
4. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of the corneal nerve. *J Cell Physiol*. 2017;232:717-724.
5. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2018;8:571-579.
6. Dana R, Farid M, Gupta PK, et al. Expert consensus on the identification, diagnosis, and treatment of neurotrophic keratopathy. *BMC Ophthalmology*. 2021;21:327-335
7. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Progress in Retinal and Eye Research*. 2018;16:107-131.
8. Vesura P, Giannaccare G, Pellegrini M, et al. Neurotrophic keratitis: current challenges and future prospects. *Eye and Brain*. 2018;10:37-45.
9. Vera-Duarte GR, Jimenez-Collado D, Kahuam-Lopez N, et al. Neurotrophic keratopathy: general features and new therapies. *Surv Ophthalmol*. 2024.69:789-804.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** coverage policy title from "Cenegermin Ophthalmic Solution" to "Ophthalmology – Oxervate." **Neurotrophic Keratitis.** <u>Initial treatment:</u> **Removed** criterion screening for "stage 2 (moderate) or stage 3 (severe) neurotrophic keratitis". <u>Recurrence treatment:</u> **Removed** criterion screening for **"**Attestation of need for additional course of therapy based upon partial response or recurrence**".** **Added** criterion screening for "The medication is prescribed by an ophthalmologist or optometrist".	11/1/2024

Annual Revision	**Neurotrophic Keratitis.** For initial therapy, the word "previously" was removed from the number of weeks of treatment received. A Note was added to clarify that each course of Oxervate is 8 weeks is added. For recurrence, the word "previously" was removed from the number of weeks of treatment received and the duration "> 8 weeks and < 16 weeks" was revised to < 16 weeks. A Note that "Each course of Oxervate for the treatment of recurrent neurotrophic keratitis is 8 weeks; total of 16 weeks for initial and recurrent neurotrophic keratitis" was added.	10/1/2025
Selected Revision	**Neurotrophic Keratitis:** The Note was revised to indicate if the patient has already received at least 8 weeks of treatment in the affected eye, review under "Patient Who Has Previously Received Oxervate". Previously, it stated to review under "Recurrence". • The term "Initial Course" is now "Initial Therapy" and the term "Recurrence" is now "Patient Who Has Previously Received Oxervate". • Initial Therapy, the Note regarding approval of up to 8 weeks per affected eye(s) was clarified: "If the patient has started treatment but did not receive 8 weeks, approve enough Oxervate to complete 8 weeks of treatment"; previously the note provided an example of approving 6 weeks for a patient who had already received 2 weeks of treatment. The Note for the requirement that patient has received < 8 weeks of treatment in the affected eye(s) was clarified such that the 8 weeks is for initial neurotrophic keratitis and it's per affected eye(s). The new Note reads: Each course of Oxervate for the treatment of initial neurotrophic keratitis is 8 weeks (per affected eye[s]). • Patient Who Has Previously Received Oxervate, the Note regarding approval of up to 8 weeks per affected eye(s) was clarified: "If the patient has started treatment but did not receive 8 weeks, approve enough Oxervate to complete 8 weeks of treatment"; previously, the note stated that if the patient already received 8 weeks of treatment, an additional 8 weeks may be approved, for a total of 16 weeks of treatment. The requirement that the patient has received < 16 weeks of treatment per affected eye(s) was revised to include the qualifiers "total" and "per lifetime"; the new requirement reads: Patient has received < 16 weeks (total) of treatment per affected eye(s) [per lifetime]. The Note was clarified that a total of two 8-week treatment courses can be approved for initial and recurrent neurotrophic keratitis per affected eye(s) per lifetime; previously, the note stated a total of 16 weeks for initial and recurrent neurotrophic keratitis. A new requirement that the patient has recurrence of neurotrophic keratitis was added. **Conditions Not Recommended for Approval**, for Treatment duration of > 16 weeks per affected eye(s) per episode, the term "per lifetime" replaced the term "per episode" and "total" was added; it now reads: Treatment	11/1/2025

	Duration of > 16 weeks Total Per Affected Eye(s) Per Lifetime. **Policy Statement.** The statement that a total of 16 weeks of Oxervate can be approved for treatment of initial and recurrent neurotrophic keratitis was clarified that this is per lifetime and that the 16 weeks entails two 8-week treatment courses.	

The policy effective date is in force until updated or retired.