Neurotrophic Keratitis Prior Authorization with Quantity Limit Program Summary

This program applies to Medicaid.

The BCBS MN Step Therapy Supplement applies to this program for Medicaid.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
10/1/2023	7/1/2019

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Oxervate® (cenegermin-bkbj) Ophthalmic solution	Treatment of neurotrophic keratitis		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Neurotrophic Keratitis(2,3)	Neurotrophic keratitis (NK) is a degenerative disease that is characterized by a reduction or absence of corneal sensitivity, due to impaired innervation by the trigeminal nerve. The lack of innervation leads to corneal epithelial breakdown, impairment of healing, and development of corneal ulceration, melting, and perforation. There are numerous underlying ocular and systemic conditions associated with NK, with the most common causes including infection (e.g., herpes simplex, herpes zoster, leprosy), trigeminal nerve palsy (e.g., surgery, neoplasia, aneurysms, facial trauma), toxicity (e.g., topical ocular anesthetics, timolol, betaxolol, sulfacetamide, diclofenac sodium, chemical burns), and systemic disease (e.g., diabetes, vitamin A deficiency, multiple sclerosis). Diagnosing NK requires clinical history and ocular examination. The presence of persistent epithelial defects (PED), ulceration, and decreased corneal sensitivity are hallmarks of disease. Corneal sensitivity testing is recommended using a cotton swab, the Cochet-Bonnet contact esthesiometer, or the CRCERT-Belmonte non-contact esthesiometer. If sensitivity testing indicates reduced sensitivity, then corneal staining, Schirmer testing, microbiology exams, lid evaluation, nerve imaging, and limbal evaluation are recommended to determine disease staging and determine underlying etiology. The clinical classification of NK is broken down into three stages. Stage 1 is characterized by corneal epithelial changes with dry and cloudy epithelium, the presence of superficial punctate keratopathy, and corneal edema. Stage 2 is characterized by recurrent and/or PED with an oval or circular shape, mostly localized at the superior half of the cornea. Stage 3 is characterized by corneal ulcer with stromal involvement that may be complicated by stromal melting and progression to corneal perforation.

	Management of NK requires any topical preservative containing medication to be discontinued if possible. All ocular surface-associated diseases (e.g., keratitis, dry eye, blepharitis, limbal stem cell deficiency) should be treated. Topical non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in NK as they inhibit the healing process. Treatment options are determined based on staging. Stage 1 is treated with preservative-free artificial tears and lubricant ointments. Therapeutic soft contact lenses, punctal plugs, and autologous serum could also be options in some cases. Oxervate can be considered in patients that fail to respond to these therapies. Stage 2 treatment includes continuing preservative-free artificial tears and lubricant ointments with prophylactic antibiotic drops. Additional treatment options for stage 2 are therapeutic soft contact lenses, topical autologous serum application, amniotic membrane grafting, conjunctival flap, tarsorrhaphy or botulinum induced ptosis, and topical nerve growth factor application. Treatment for stage 3 includes all of the treatments for stage 2 with the addition of N-acetylcysteine, oral tetracycline, and medroxyprogesterone. Surgical treatments are typically reserved for refractory cases. Corneal perforations require immediate treatment with either cyanoacrylate glue and soft bandage contact lenses, or amniotic membrane grafting. Tectonic perforating or lamellar keratoplasty can be performed for larger perforations.
Efficacy(1,4)	Cenegermin ophthalmic solution contains cenegermin, a recombinant form of human nerve growth factor produced in Escherichia coli. 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. Efficacy and safety of Oxervate (cenegermin 20 mcg/mL) for treatment of patients with NK (N=151) was evaluated in two Phase 2, 8-week, randomized, multi-center, double-masked, vehicle-controlled studies (Study NGF0212 and Study NGF0214). In both studies, cenegermin was dosed 6 times daily in the affected eye(s) for 8 weeks. Results for the primary endpoint, "complete corneal healing" (i.e., absence of corneal lesion staining and no persistent staining in the rest of the cornea after 8 weeks of treatment) were as follows: • Study NGF0214- cenegermin 20 mcg/mL (65.2%); vehicle (16.7%) [treatment difference: 48.6%; 95% CI: 24%, 73.1%; p-value less than 0.01] • Study NGF0212- cenegermin 20 mcg/mL (72.0%); vehicle (33.3%) [treatment difference: 38.7%; 95% CI: 20.7%, 56.6%; p-value less than 0.01] In patients healed after 8 weeks of Oxervate (cenegermin 20 mcg/mL) therapy, recurrences occurred in about 20% of patients in Study NGF0212 and 14% of patients in Study NGF0214. Least square mean changes (improvement) from baseline in corneal sensitivity inside the lesion after 8 weeks of treatment were not clinically significant in either study: • Study NGF0214- cenegermin 20 mcg/mL (1.6); vehicle (0.7) [treatment difference: 0.9; 95% CI: 0.2, 1.7] • Study NGF0212- cenegermin 20 mcg/mL (1.1); vehicle (0.8) [treatment difference: 0.3; 95% CI: -0.4, 0.9] Inclusion criteria required patients to be 18 years of age with Stage 2 (persistent epithelial defect [PED]) or Stage 3 (corneal ulcer) NK (involving one eye for NGF0212 and involving both eyes for NGF0214); PED or corneal ulceration of greater than 2 weeks duration refractory to greater than 1 conventional non-surgical treatments for NK (e.g., preservative-free artificial tears, gels or ointments; discontinuation of preserved topical drops and medications that can decrease corneal sensitivity; therapeutic contact lenses); evidence of decreased corneal sensitivity (less than or equal to 4 cm on Cochet-Bonnet aesthesiometer) within area of the PED or corneal ulcer and outside of the area of the defect in greater than 1 corneal quadrant; best corrected distance visual acuity (BCDVA) score less than or equal to 75 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, (greater than or equal to +0.2 log MAR, less than or equal to 20/32 Snellen or less than or equal to 0.625 decimal

	fraction) in the affected eye; and no objective clinical evidence of improvement in PED or corneal ulceration within the 2 weeks prior to study enrollment. Exclusion criteria included any active ocular infection or active ocular inflammation not related to NK in the affected eye; any other ocular disease requiring topical ocular treatment in the affected eye during study treatment period; severe vision loss in the affected eye with no potential for visual improvement; Schirmer's test without anesthesia less than or equal to 3 mm/ 5 minutes in the affected eye; severe blepharitis and/or severe meibomian gland disease in the affected eye; history of any ocular surgery in affected eye within 3 months before study enrollment (allowed if the ocular surgery was the cause of Stage 2 or 3 NK); prior surgical procedure(s) for treatment of NK (e.g., complete tarsorrhaphy, conjunctival flap, etc.) in affected eye; previous Botox treatment; botulinum injections used to induce pharmacologic blepharoptosis eligible only if last injection was greater than 90 days prior to enrollment; use of contact lenses during study treatment periods in the eye with NK; anticipated need for punctal occlusion during study treatment period (patients with punctal occlusion or punctal plugs inserted prior to study were eligible for enrollment if the punctal occlusion was maintained during the study); evidence of corneal ulceration involving posterior third of the corneal stroma, corneal melting or perforation in the affected eye; presence/history of any ocular or systemic disorder or condition that might have hindered efficacy of the study treatment or its evaluation; need for or anticipated change in dose of systemic medications known to impair function of the trigeminal nerve (e.g., neuroleptics, antipsychotic and antihistamine drugs [these treatments were allowed during the study if initiated prior to 30 days before study enrollment provided they remained stable throughout the course of the study treatment periods]); known hypersensitivity to study or procedural medications (e.g., fluorescein); history of drug, medication or alcohol abuse or addiction; use of any investigational agent within 4 weeks of baseline visit; and participation in another clinical study at the same time as the present study.
Safety(1)	Oxervate does not have any FDA labeled contraindications for use.

REFERENCES

Number	Reference
1	Oxervate prescribing information. Dompé farmaceutici S.p.A. October 2019.
2	Rabiolo, A., Rama, P., Ferrari, G., et al. (2017, July 09). Neurotrophic Keratitis. Last updated October 2022. http://eyewiki.aao.org/Neurotrophic_Keratitis.
3	Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clin Ophthalmol. 2014;8:571-9. Published 2014 Mar 19. doi:10.2147/OPTH.S45921.
4	Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. Ophthalmology 2018; 125:1332-1343.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Oxervate	cenegermin-bkbj ophth soln	0.002 %	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Oxervate	Cenegermin-bkbj Ophth Soln 0.002% (20 MCG/ML)	0.002 %	56	Vials	56	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Oxervate	cenegermin-bkbj ophth soln	0.002 %	Medicaid

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Oxervate	Cenegermin-bkbj Ophth Soln 0.002% (20 MCG/ML)	0.002 %	Medicaid

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of neurotrophic keratitis (NK) **AND** 2. The patient has stage 2 (persistent epithelial defect [PED]) or stage 3 (corneal ulcer) NK **AND** 3. ONE of the following: A. The patient has NOT been previously treated with the requested agent in the affected eye(s) AND ALL of the following: 1. The patient's PED and/or corneal ulcer have been present for at least 2 weeks **AND** 2. ONE of the following: A. The patient's NK has been refractory to at least ONE conventional non-surgical treatment (i.e., preservative-free lubricant eye drops or ointment, discontinuation of preserved topical agents that can decrease corneal sensitivity, therapeutic soft contact lenses, topical autologous serum application, botulinum A toxin treatment) **OR** B. The patient has an intolerance or hypersensitivity to at least ONE conventional non-surgical treatment for NK **OR**

Module	Clinical Criteria for Approval
	C. The patient has an FDA labeled contraindication to ALL conventional non-surgical treatments for NK **OR** D. The patient's medication history includes at least ONE conventional non-surgical treatment (i.e., preservative-free lubricant eye drops or ointment, discontinuation of preserved topical agents that can decrease corneal sensitivity, therapeutic soft contact lenses, topical autologous serum application, botulinum A toxin treatment) AND ONE of the following: 1. The conventional non-surgical treatment was discontinued due to lack of effectiveness or an adverse event **OR** 2. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over conventional non-surgical treatment **OR** E. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** F. The prescriber has provided documentation that ALL conventional non-surgical treatments for NK cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** 3. The patient has decreased corneal sensitivity within the area of the PED or ulcer and outside the area of defect in at least one corneal quadrant **OR** B. The patient has been previously treated with the requested agent in the affected eye(s) AND BOTH of the following: 1. The patient had complete corneal healing in the previously treated eye(s) **AND** 2. The patient has a recurrence of neurotrophic keratitis (NK) that requires another treatment course **AND** 4. ONE of the following: A. The patient does NOT have ocular surface disease(s) associated with or in conjunction with NK **OR** B. BOTH of the following: 1. The patient has ocular surface disease(s) associated with or in conjunction with NK **AND** 2. The ocular surface disease(s) has been properly treated **AND** 5. The patient will NOT be using the requested agent in combination with a topical ophthalmic NSAID **AND** 6. The patient does NOT have any of the following: A. Active ocular infection or active ocular inflammation not related to NK in the affected eye **OR** B. Severe blepharitis and/or severe Meibomian gland disease in the affected eye **OR** C. History of any ocular surgery in the affected eye within the past 90 days that has not been determined to be the cause of NK **OR** D. Corneal perforation, ulceration involving the posterior third of the corneal stroma, or corneal melting **AND** 7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., optometrist, ophthalmologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 8 weeks

Module	Clinical Criteria for Approval
	NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. BOTH of the following: A. The patient has bilateral NK **AND** B. The requested quantity (dose) does NOT exceed TWICE the program quantity limit **Length of Approval**: 8 weeks