Drug Use Research & Management Program
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New Drug Evaluation: cenegermin, ophthalmic solution

Date of Review: December 2020
Generic Name: cenegermin-bkbj

End Date of Literature Search: 09/30/20
Brand Name (Manufacturer): Oxervate™ (Dompé U.S. Inc)

Research Questions:
1. Is there comparative evidence that cenegermin is more effective or safer than current standard of care in the treatment of neurotrophic keratitis?
2. Are there subpopulations of patients for which cenegermin may be more effective or associated with less harm in the treatment of neurotrophic keratitis?

Conclusions:
- There is moderate quality evidence that for patients with stage 2 or 3 neurotrophic keratitis (NK), cenegermin improves corneal healing compared with vehicle at 8 weeks.[1,2]
- There is low quality evidence that cenegermin does not improve corneal sensitivity, vision or quality of life at 8 weeks. There is insufficient evidence to make conclusions about cenegermin's effects on disease progression and deterioration of disease. Long term data is not available to assess these clinical outcomes.
- There is insufficient evidence comparing cenegermin to other treatments commonly used in stage 2 or 3 NK.

Recommendations:
- Make cenegermin non-preferred and apply prior authorization criteria (**Appendix 2**).

Background:
Neurotrophic keratitis (NK) is a rare degenerative corneal disease caused by impairment in the first branch of the trigeminal nerve. The trigeminal nerve provides the cornea with sensation and triggers blinking and tear production in response to stimuli.[3] This sensory innervation protects the cornea from damage. Neurotrophic keratitis causes a reduction in corneal sensitivity which makes the cornea more prone to damage and poor wound healing, which can result in ulcers and perforation.[4] Some causes of NK include herpetic keratitis, intracranial lesions, and neurosurgical procedures that damage the trigeminal nerve.[4] Less common causes include chemical burns, physical injuries, corneal dystrophy, chronic use of topical eye medications (e.g. anesthetics, topical beta blockers, and ketorolac), and systemic conditions such as diabetes mellitus and multiple sclerosis. The estimated prevalence is less than 5 cases per 10,000 persons.[5] There were no previous FDA approved pharmacologic treatments for NK. Those who develop NK rarely report symptoms since there is an absence of corneal sensation, but it can eventually lead to vision loss. Treatment options vary widely and are based on disease severity (**Table 1**). Treatment options are supportive and do not address the underlying cause or improve the speed of healing. The goal of treatment is to slow disease progression, increase corneal sensitivity, and prevent vision loss. Cenegermin is a recombinant human nerve growth factor indicated as an ophthalmic solution for the treatment of NK.[6] The goal is to restore corneal integrity through re-innervation and corneal healing.[3] Due to a lack of long-term data and because it did not meeting cost-effectiveness criteria,

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the National Institute for Health and Care Excellence (NICE) did not approve cenegermin for treatment in the United Kingdom.[7] The recommended dose is 6 total drops per day (every 2 hours) for 8 weeks. There are administration and storage requirements that may be challenging. It requires refrigeration by the patient and has a multistep administration procedure involving several components, including one drug vial, one adapter, six pipettes and six disinfectant wipes for one day of therapy.[6]

Table 1: Clinical presentation and treatment options for neurotrophic keratitis

Disease Stage	Clinical Presentation	Standard of Care
Stage 1 (mild disease)	Corneal epithelial changes	Artificial tears, autologous serum eye drops, discontinue toxic topical medications
Stage 2 (moderate disease)	Persistent nonhealing epithelial defects, possible decrease in vision	Therapeutic contact lenses
Stage 3 (severe disease)	Corneal ulceration and stromal involvement, possible pain	Surgical intervention (tarsorrhaphy, amniotic membrane transplantation, conjunctival flap)

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Cenegermin ophthalmic solution (20 mcg/ml dosed 6-times daily) was approved based on two phase II trials that were similar in design (**Table 3**).[1,2] Both were double-masked, vehicle-controlled, randomized controlled trials including patients with stage 2 or 3 (moderate or severe) NK. One study was conducted in Europe[1] and the other in the United States[2]. The most common underlying causes were herpetic eye disease, dry eye disease, ocular surgery, diabetes mellitus and surface injury/inflammation. The most common previous therapies were topical antibacterials and artificial tears.[5] The primary outcome was corneal healing, defined as less than 0.5 mm fluorescein staining in the lesion area at 4 or 8 weeks. However, the FDA requested a post-hoc analysis of a more conservative definition of corneal healing (no residual fluorescein staining and no persistent staining elsewhere in the cornea).[5] After an 8 week double-masked treatment period, patients were eligible for a 24 or 48 week follow-up period.

In both trials, more patients receiving both doses of cenegermin experienced corneal healing compared to those receiving the vehicle control (**Table 3**). This was observed at week 4 and week 8. Complete healing (0 mm in lesion area) was achieved by 49% of patients in the 10 mcg/ml and 58% in the 20 mcg/ml groups compared to 13% in the vehicle group in the study by Bonini et al.[1] The treatment differences were statistically significant compared to vehicle for both doses. A NICE meta-analysis of corneal healing at 8 weeks demonstrated a statistically significant effect with the initial definition (<0.5 mm) (OR 4.24; 95% CI 2.11-8.50; p<0.001) and with the more conservative definition (0 mm in the lesion area) (OR 6.09; 95% CI 2.97-12.50; p<0.001).[7]

There was no significant difference in corneal sensitivity between cenegermin and vehicle in either study, measured using the Cochet-Bonnet esthesiometer.[5] With decreased corneal sensitivity, the blinking and tearing mechanism is reduced, leaving the cornea exposed and prone to damage. There was also no significant difference in vision between treatment and vehicle, as measured by the change from baseline in best-corrected distance visual acuity (BCDVA) score on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. A post-hoc analysis suggested fewer patients experienced disease progression with cenegermin (22%) compared to vehicle (50%).[2] Follow up to 24 weeks and 48 weeks suggested a high proportion of patients continued to experience corneal healing. However, recurrence rates were more frequent for the cenegermin 10 mcg/ml group (17%) and 20 mcg/ml (20%) compared to the vehicle (10%).[1]

Recurrence is defined as stage 2 or stage 3 NK after complete healing has occurred and the treatment has stopped.[5] In the Pflugfelder et al study, 56.5% of patients in the cenegermin group (20 mcg/ml) compared to 20.8% in the vehicle group achieved complete corneal healing.[2]

There is a lack of evidence comparing cenegermin with any other active comparator other than vehicle. While this was meant to be similar to artificial tears, other clinical interventions are often used in stage 2 and 3 NK. Artificial tears are typically given every 2-4 hours to help improve corneal surface at all disease stages. Additionally, there were no significant differences in vision improvement, corneal sensitivity or quality of life between cenegermin and vehicle. The median baseline lesion size in the study by Plugfelder et al. was 3.1 (95% CI 0.53 to 8.23) in the treatment group compared to 2.99 (95% CI 0.23 to 6.10) in the vehicle group. [2] However, this information was not available in the study by Bonini et al. [1] It remains unknown if treatment with cenegermin will be effective for NK due to all underlying causes or not. Additional limitations include a small number of patients studied, high withdrawal rates, and limited long term follow up data.

Clinical Safety:
Cenegermin has negligible systemic absorption and major systemic side effects are not common and were not different between the groups. There were no serious adverse events or deaths considered to be related to study treatment.[6] Most adverse events in clinical trials were mild and transient. The most common reason for discontinuation due to adverse events was disease progression and reduced visual acuity rather than adverse events related to cenegermin.[5] In total from both studies, there were 38 adverse events (the majority were eye-disorder related) in the vehicle group (50%) and 48 in the approved cenegermin dose (20 mcg/ml) (64%).[5] The adverse events that occurred more frequently in the cenegermin group were cataract, corneal deposits, corneal graft rejection, eye inflammation, eye pain, foreign body sensation, lacrimation increased, ocular hyperemia, visual acuity reduced and intraocular pressure increased.[5]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Vision loss
2) Disease progression
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Corneal healing (less than 0.5 mm fluorescein staining in the lesion area) at week 4 or 8
2) Completely healed (0—mm lesion staining and no other persistent staining) at week 4 or 8 (post-hoc analysis)

Table 2. Pharmacology and Pharmacokinetic Properties.[6]

Parameter	
Mechanism of Action	Cenegermin is a nerve growth factor involved in the differentiation and maintenance of neurons, which acts through nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.
Oral Bioavailability	N/A (ophthalmic solution); negligible systemic absorption
Distribution and Protein Binding	N/A (ophthalmic solution); not distributed throughout the body
Elimination	N/A (ophthalmic solution)
Half-Life	N/A (ophthalmic solution)
Metabolism	N/A (ophthalmic solution)

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1.Bonini et al.[1] Phase II, DM, MC, PG, RCT	1. Cenegermin 10 ug/ml 6 drops/day 2. Cenegermin 20 ug/ml 6 drops/day 3. Vehicle Control 8 weeks	Demographics: Adults with stage 2 or stage 3 NK • Mean 61 years • 61% female • 91% white • Median lesion size 3.10 mm Key Inclusion Criteria: Stage 2 or 3 NK, Decreased corneal sensitivity BCDVA score of 75 ETDRS letters or fewer, no objective clinical evidence of improvement Key Exclusion Criteria: stage 2 or 3 NK in both eyes, active ocular infection or inflammation, other ocular disease or severe vision loss in the affected eye, history of drug or alcohol abuse	ITT: 1. 52 2. 52 3. 52 PP: 1. 46 2. 40 3. 40 Attrition: 1 .6 (11.5%) 2. 12 (23%) 3. 4 (8%)	Corneal healing at week 4 1. 28 (54.9%) 2. 29 (58%) 3. 10 (19.6%) *Treatment Difference* 1 vs. 3: +35.3%; 97% CI 15.88% to 54.7%; p< 0.001 2 vs. 3: +38.4%; 97% CI 18.96% to 57.83%; p<0.001 Completely healed at week 4 1. 25 (49%) 2. 29 (58%) 3. 7 (13.7%) *Treatment Difference* 1 vs. 3: +35.3%; 97% CI 16.78% to 53.8%; p< 0.001 2 vs. 3: +44.3%; 97% CI 25.8% to 62.75%; p<0.001	ARR 35% / NNT 3 ARR 38% / NNT 3 ARR 35% / NNT 3 ARR 44% / NNT 3	Discontinuation due to AE: 1. 3 (5.8%) 2. 9 (17.3%) 3. 1 (19%) P values not provided	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear; differences in baseline population including underlying cause and prior treatment history. Details of randomization methods not available. Performance Bias: low; patients, investigators and site/sponsor staff were masked to treatment and dosage Detection Bias: low; masked central analysis for efficacy outcome Attrition Bias: unclear; efficacy analyses performed on ITT population with LOCF method, but high and unbalanced rates of attrition Reporting Bias: low; primary outcome requested to be changed by FDA and reported post-hoc Other Bias: high; The trial was supported by Dompe pharmaceuticals, who participated in the design and conduct of the study, data collection, analysis and preparation of the manuscript. All seven authors disclosed financial conflicts with the drug manufacturer. **Applicability**: Patient: Total number of patients studied remains low. Efficacy in patients with stage 1 disease is unknown. Intervention: No dose response identified Comparator: Vehicle was similar to artificial tears, lack of evidence comparing cenegermin with any other comparator often used with artificial tears Outcomes: Commonly used outcome in ocular clinical studies Setting: multicenter in 39 sites in 9 European countries (Belgium, France, Germany, Hungary Italy, Poland, Portugal, Spain and the United Kingdom)

2. Pflugfelder, et al.[2] Phase II, DM, MC, PG, RCT	1. Cenegermin 20 ug/ml 6 drops/day 2. Vehicle Control 8 weeks	Demographics: Adults with stage 2 or stage 3 NK • Mean 65 years • 60% female • 83% white Key Inclusion Criteria: Stage 2 or 3 NK, Decreased corneal sensitivity BCDVA score of 75 ETDRS letters or fewer, no objective clinical evidence of improvement Key Exclusion Criteria: active ocular infection or inflammation, other ocular disease or severe vision loss in the affected eye, history of drug or alcohol abuse	ITT: 1. 24 2. 24 PP: 1. 18 2. 15 Attrition: 1. 6 (25%) 2. 9 (37.5%)	Corneal healing at week 8 1. 15 (62.5%) 2. 6 (25%) *Treatment Difference* +37.5%; 95% CI 11.5% to 63.5%; p< 0.001 Completely healed at week 8 1. 15 (65.2%) 2. 4 (16.7%) *Treatment Difference* +48.6%; 95% CI 24% to 73.1%; p< 0.001	ARR 38% / NNT 3 ARR 48% / NNT 2	Discontinuation due to AE: 1. 4 (17.4%) 2. 3 (12.5%) P values not provided	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: low; appropriate randomization and allocation concealment methods; more stage 3 patients in the treatment group (37.5% vs. 25%) Performance Bias: low; patients, investigators and site/sponsor staff were masked to treatment and dosage Detection Bias: low; masked central analysis for efficacy outcome Attrition Bias: unclear; efficacy analyses performed on ITT population with LOCF method, but high and unbalanced rates of attrition Reporting Bias: low; primary outcome requested to be changed by FDA and reported post-hoc Other Bias: high; The trial was supported by Dompe pharmaceuticals, who participated in the design and conduct of the study, data collection, analysis and preparation of the manuscript. Eight authors disclosed financial conflicts with the drug manufacturer. **Applicability**: Patient: Total number of patients studied remains low Intervention: No dose response identified Comparator: Vehicle and treatment contained the antioxidant methionine as a stabilizer, lack of evidence comparing cenegermin with any other comparator often used in combination with artificial tears Outcomes: Commonly used outcome in ocular clinical studies Setting: multicenter in 11 sites in the United States

Abbreviations [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; BCDVA = best-corrected distance visual acuity; CI = confidence interval; DM = double-masked; ETDRS = early treatment diabetic retinopathy study; ITT = intention to treat; LOCF = last observation carried forward; MC = multicenter; N = number of subjects; NA = not applicable; NK = neurotrophic keratitis; NNH = number needed to harm; NNT = number needed to treat; PG= parallel group; PP = per protocol.

References:

1. 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(9):1332-1343.
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(1):14-26.
3. Deeks ED, Lamb YN. Cenegermin: A Review in Neurotrophic Keratitis. *Drugs.* 2020;80(5):489-494.
4. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579.
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6. Oxervate (cenegermin-bkbj) prescribing information. Dompe Inc. October 2019. Availalbe at: https://oxervate.com/wp-content/uploads/2020/05/OXERVATE_Prescribing_Information_102019.pdf.
7. Fleeman N, Mahon J, Nevitt S, et al. Cenegermin for Treating Neurotrophic Keratitis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *Pharmacoecon Open.* 2019;3(4):453-461.

Appendix 1: Prescribing Information Highlights

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

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

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

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

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

----------CONTRAINDICATIONS----------
None. (4)
----------WARNINGS AND PRECAUTIONS----------
Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion. (5.1)

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

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

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

Revised: 8/2018

Cenegermin-bkbj (Oxervate™)

Goal(s):

- Ensure medically appropriate use of cenegermin

Length of Authorization:

8 weeks

Requires PA:

- Cenegermin-bkbj (Oxervate™)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy?	**Yes**: Pass to RPh. Deny; medical appropriateness Cenegermin is only approved for 8 weeks of therapy	**No:** Go to #3
3. Is this for the treatment of Stage 2 or 3 neurotrophic keratitis?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is it prescribed by or in consultation with an ophthalmologist?	**Yes:** Approve for 8 weeks	**No:** Pass to RPh. Deny; medical appropriateness