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CADTH Reimbursement Recommendation

Cenegermin (Oxervate)

Indication: For the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults

Sponsor: Dompé Farmaceutici S.p.A

Final recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Oxervate?

CADTH recommends that Oxervate be reimbursed by public drug plans for the treatment of moderate to severe neurotrophic keratitis (NK) in adult patients if certain conditions are met.

Which Patients Are Eligible for Coverage?

Oxervate should only be covered to treat patients who have never been treated with Oxervate before and have previously tried but failed conventional nonsurgical therapies.

What Are the Conditions for Reimbursement?

Oxervate should only be reimbursed if prescribed by a cornea specialist experienced in the management of NK or by an ophthalmologist when comanaging the patient with a cornea specialist. Oxervate should not be prescribed along with preservative-containing topical antibiotics and/or antiviral eye drops. The cost of Oxervate should be reduced.

Why Did CADTH Make This Recommendation?

- In patients with NK, 2 clinical trials showed that treatment with Oxervate was better for healing the corneal (the clear outer layer of the eye) than treatment with the vehicle control.
- Corneal healing was an important need, according to patients, and Oxervate meets this need.
- Based on CADTH's assessment of the health economic evidence, Oxervate does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Over 3 years Oxervate is expected to increase drug costs to the public drug plans by $42,681,030.

Additional Information

What is Neurotrophic Keratitis?

NK is a rare and gradually worsening disease of the cornea. Moderate and severe NK can greatly affect patients' vision and adversely impact their health-related quality of life. Approximately 6,100 people in Canada were diagnosed with NK in 2021, and 2,300 of them have moderate or severe disease.

Unmet Needs in Neurotrophic Keratitis

Patients may not respond to currently available treatments for moderate to severe NK. Some treatment options are associated with complications (such as surgeries) or cosmetic issues (such as a permanent tarsorrhaphy).

How Much Does Oxervate Cost?

Treatment with Oxervate is expected to cost approximately $118,230 per full 8-week course.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that cenegermin be reimbursed for the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) NK in adults, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In 2 randomized, double-blind, phase II, vehicle-controlled studies (NGF0212, N = 156; NGF0214, N = 48) in adult patients with moderate to severe NK, statistically significantly more patients treated with cenegermin exhibited corneal healing than patients who were treated with vehicle. In the NGF0212 study, corneal healing at week 4 was reported in 29 patients (58.0%) in the cenegermin group and 10 patients (19.6%) in the vehicle control group (between-group difference of 38.4%; 97.06% confidence interval [CI], 18.96 to 57.83; P < 0.001). In the NGF0214 study, corneal healing at week 8 was reported in 16 patients (69.6%) in the cenegermin group and 7 patients (29.2%) in the vehicle group (between-group difference of 40.4%; 95% CI, 14.2 to 66.6; P = 0.006). However, the effect of cenegermin on patients' health-related quality of life (HRQoL), disease deterioration, and disease relapse remain uncertain. CDEC concluded that cenegermin met some of the needs identified by patients by achieving corneal healing in some patients without relying on surgical intervention. Although patients identified the need for a treatment that would also reduce the burden of NK, and improve HRQoL, evidence was not available for these outcomes.

Using the sponsor-submitted price for cenegermin, the incremental cost-effectiveness ratio for cenegermin was $1,368,740 per quality-adjusted life-year (QALY) compared with surgical tarsorrhaphy. Cenegermin was dominated by amniotic membrane transplant (AMT) due to lack of additional benefit (i.e., both treatments provided the same number of QALYs, and AMT costs were $114,597 lower). Cenegermin is therefore not cost-effective at a $50,000 per QALY willingness-to-pay threshold for the indicated Health Canada population. A reduction in price of at least 95% is required for cenegermin to be considered cost-effective.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must have failed conventional nonsurgical therapies.	In studies NGF0212 and NGF0214, treatment with cenegermin demonstrated a clinical benefit in patients who were refractory to 1 or more conventional nonsurgical treatments for NK, such as preservative-free artificial tears, gels, or ointments.	Appropriate nonsurgical supportive therapies must be provided before patients are eligible for cenegermin. Nonsurgical supportive therapies include (but are not limited to) preservative-free artificial tears, autologous serum tears, etiology-specific treatments (e.g., antivirals), punctal occlusion, and bandage contact lenses. Removal of offending drugs (e.g., preservative-containing eye drops) should occur if possible.

Reimbursement condition	Reason	Implementation guidance
		If the patients do not respond well to appropriate treatment options within a period of 1 to 2 months of close monitoring and treatment, it would be reasonable to offer them cenegermin in the next step. Where lack of response is defined as not achieving complete resolution (i.e., 0 mm in size) or significant closure (i.e., less than 0.5 mm in size) of the epithelial defect.
2. Patients must not have had prior treatment with cenegermin (with or without treatment success).	No conclusion can be drawn from the evidence to support whether or not re-treatment with a subsequent course of cenegermin is beneficial.	—
Renewal		
3. The maximum duration of authorization of cenegermin should be 8 weeks without the option for renewal.	There is a lack of clinical evidence for repeated use or prolonged use beyond the initial 8-week treatment course, regardless of treatment response.	—
Prescribing		
4. The patient must be under the care of a cornea specialist with experience in the diagnosis and management of NK, or under the care of an ophthalmologist when comanaging the patient with a cornea specialist.	Accurate diagnosis and follow-up of patients with NK are important to ensure that cenegermin is prescribed to the most appropriate patients.	Given the intense administration schedule of cenegermin, CDEC noted that there is a need for patients to receive appropriate training and/or resources regarding proper administration and storage of cenegermin. CDEC recommends that the sponsor be required to cover the cost of the training and/or the resources required for the safe and effective use of cenegermin.
5. Cenegermin must not be prescribed in conjunction with topical ophthalmic medications other than preservative-free topical antibiotics and/or preservative-free topical antiviral eye drops.	No evidence was identified to demonstrate an additional benefit of cenegermin in conjunction with other topical ophthalmic treatments. Upon enrolment in study NGF0212 and study NGF0214, patients were required to discontinue all topical ophthalmic medications.	—
Pricing		
6. A reduction in price.	In the CADTH base case, cenegermin is dominated by AMT due to the lack of additional clinical benefit (and it is associated with greater costs). When compared to surgical tarsorrhaphy, cenegermin is associated with an ICER of $1,368,740 per QALY gained, although there is uncertainty regarding the degree of any incremental benefit relative to surgical alternatives.	—

Reimbursement condition	Reason	Implementation guidance
	As such, a price reduction of at least 95% would be required to achieve cost-effectiveness at a $50,000 per QALY threshold. A price reduction, up to 97%, may be required to account for uncertainty in the degree of disutility associated with surgical tarsorrhaphy, as well as to ensure similar costs to AMT.	

AMT = amniotic membrane transplant; CDEC = Canadian Drug Expert Committee; ICER = incremental cost-effectiveness ratio; NK = neurotropic keratitis; QALY = quality-adjusted life-year.

Discussion Points

- The appropriate place in therapy of cenegermin is uncertain. In both studies, even though all patients received prior treatment for moderate to severe NK, the number, sequence, and duration of previous treatments are unknown.
- There is a lack of direct and indirect evidence to compare cenegermin with other active treatments, including surgery, for the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) NK in adult patients.
- To provide equitable access to cenegermin in communities without a corneal specialist, CDEC discussed that collaboration between a corneal specialist and a local ophthalmologist should be considered.
- CDEC discussed that the administration regimen and storage requirements may not be feasible for all patients and that prescribers should consider the likelihood of patient adherence when offering cenegermin.
- CDEC discussed that patients who fail appropriate conventional nonsurgical therapies should have the opportunity to be assessed for surgery before prescribing cenegermin.
- CDEC discussed the potential for use of cenegermin beyond the approved indication in less severe NK, such as mild NK. A cornea specialist must be involved in the patient's care to ensure that cenegermin is prescribed appropriately to patients with moderate (persistent epithelial defect) to severe (corneal ulcer) NK.

Background

NK is a rare degenerative disorder of the cornea that is characterized by impaired corneal nerve function with subsequent corneal epitheliopathy. In 2021, approximately 6,100 people in Canada were diagnosed with NK, and 2,300 of them had moderate or severe disease.

Cenegermin has been approved by Health Canada for the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) NK in adults. It is a recombinant human nerve growth factor for topical ophthalmic use and is available as topical eye drops, 20 mcg/mL (0.002%). The recommended dose is 1 drop of cenegermin in the conjunctival sac of the affected eye(s), 6 times per day at intervals of 2 hours between drops. Treatment with cenegermin should be continued for 8 weeks.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 randomized controlled trials in adult patients with moderate to severe NK
- patients' perspectives gathered by 1 patient group, the Canadian Organization for Rare Disorders
- input from public drug plans that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with NK
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The clinical experts indicated that not all patients respond to currently available treatments for moderate to severe NK and patients may become refractory to them. Some treatment options are associated with complications or cosmetic issues.

In the experts' opinion, cenegermin has a unique mechanism of action that may cure the disease instead of being used for symptom control only. It can be used as a first-line treatment or in combination with the other currently available treatments for NK. Patients with all stages of NK are suitable for this treatment. The experts noted that it is not clear which patients would be most likely to benefit from treatment.

The experts also indicated that in clinical practice, treatment response is assessed using the size of the epithelial defect. Complete resolution (i.e., 0 mm in size) or significant closure (i.e., less than 0.5 mm in size) of the epithelial defect would be clinically meaningful. The experts suggested that during the 8-week treatment period with cenegermin, patients' progress needs to be assessed at week 4 and week 8, and again 4 weeks after the completion of the 8-week course. Follow-up time can be tailored depending on the patients' response.

The experts indicated that treatment with cenegermin should be discontinued if the patient experiences significant adverse events (AEs), or if the patient is unable to comply with the dosing schedule.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Committee response
Considerations for initiation of therapy	
Specialists experienced in this rare condition (moderate or severe NK) may be limited to urban settings. Staging, monitoring, and follow-up for this home-based therapy could be challenging.	The clinical experts noted to CDEC that access to cornea specialists is more likely in urban areas, in both academic centres and the community. As long as patients have access to care from specialists, staging, monitoring, and follow-up for the treatment of cenegermin would not be an issue. Patients in a rural setting may have difficulty in accessing a cornea specialist, which would challenge the diagnosis, monitoring, and follow-up of NK. One solution in this situation is that a local ophthalmologist may comanage the patient with a cornea specialist from a distance.
How will jurisdictions implement the requested indication of "stage 3 (severe) NK patients who have failed non-surgical treatments" when none of the other nonsurgical alternatives are indicated in this setting?	The clinical experts noted to CDEC that there are off-label nonsurgical alternatives available for patients with NK who have failed certain medical treatments. These may include preservative-free artificial tears, autologous serum tears, or removal of any offending drugs (if possible). If the patients do not respond well to these alternatives within a period of 1 to 2 months of treatment, it would be reasonable to offer them cenegermin as a next step.

CDEC = Canadian Drug Expert Committee; NK = neurotropic keratitis.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two phase II, double-blind, randomized controlled trials (NGF0212, N = 156; NGF0214, N = 48) submitted by the sponsor are included in this systematic review. The objectives of both studies were to evaluate the efficacy and safety of cenegermin eye drops in patients with moderate to severe NK. The studies included adult patients with a diagnosis of moderate or severe NK. Eligible patients were randomized to receive cenegermin or vehicle therapy for 8 weeks. At the end of the 8-week controlled treatment period, patients in study NGF0212 entered a 48- or 56-week follow-up period. The duration and treatment during the safety follow-up period was determined based on the randomized treatment they received and the healing of their persistent epithelial defect or corneal ulcer. The follow-up period was 48 weeks (approximately 12 months) for patients who were initially randomized to cenegermin (10 mcg/mL or 20 mcg/mL), regardless of whether the patient was completely healed or not completely healed at week 8. The follow-up period was also 48 weeks for patients who were initially randomized to vehicle and who were completely healed at week 8. The follow-up period was 56 weeks in length for patients who were initially randomized to vehicle and who were not completely healed at week 8. These patients were randomly assigned to treatment with cenegermin (10 mcg/mL or 20 mcg/mL) for 8 weeks. In study NGF0214, patients who completed the 8-week controlled treatment period entered a 24-week follow-up period. In both studies, all patients who were completely healed at week 8 (including those receiving active

treatment) were eligible for another course of treatment in the event of recurrence during the follow-up period. The primary efficacy outcome was the proportion of patients achieving complete corneal healing at week 4 (the NGF0212 trial) or week 8 (the NGF0214 trial) by the central reading centre. Secondary efficacy outcomes included corneal sensitivity, corneal clearing, disease deterioration, and relapse; the exploratory outcomes included HRQoL. The dose of 10 mcg/mL was not approved by Health Canada; therefore, results related to this dose were not included in this review.

In the NGF0212 study, the mean age of patients at baseline was 61 years (standard deviation [SD] = 16). In total, 39% of patients were male, 53% of patients had moderate NK, and 47% had severe NK.

In the NGF0214 study, the mean age of patients at baseline was 65 years (SD = 14). In total 39% of patients were male, 69% of patients had moderate NK, and 31% had severe NK.

Efficacy Results

In the NGF0212 trial, the complete healing of the persistent epithelial defect or corneal ulcer at week 4, as determined by the central reading centre, was achieved in 29 patients (58.0%) in the cenegermin 20 mcg/mL group and 10 patients (19.6%) in the vehicle control group. The difference in the percentage of patients who achieved complete healing at week 4 between the cenegermin 20 mcg/mL group and the vehicle control group was 38.4% (97.06% CI, 18.96% to 57.83%; P < 0.001). Treatment with cenegermin was also related to the higher rate of corneal healing compared to vehicle therapy in study NGF0214. In this study, the proportion of patients achieving complete corneal healing was 69.6% in the cenegermin-treated group versus 29.2% in the vehicle-treated group at week 8. The between-group difference in corneal healing was 40.4% (95% CI, 14.2 to 66.6; P = 0.006). The clinical experts consulted by CADTH indicated that the differences between cenegermin and vehicle are considered clinically relevant.

For the outcomes of corneal clearing and corneal sensitivity, between-group differences did not reach statistical significance. Corneal clearing was defined as grade 0 on the modified Oxford Grading Scale, which is absent of staining. According to the clinical experts consulted by CADTH, this is a more stringent measure than corneal healing (< 0.5 mm of lesion staining) in assessing treatment effect on NK.

Overall, the potential benefit of cenegermin on HRQoL remains unknown. The differences between cenegermin and vehicle in the overall composite score of the National Eye Institute Visual Function Questionnaire-25 items or the EQ-5D 5-Level health state score were not statistically significant. The relationship between the gains from corneal healing and improvement in patient's HRQoL was unclear.

There was no difference found between cenegermin and vehicle in reducing the risk of disease deterioration. For patients who had achieved complete corneal healing, 8 weeks of treatment with cenegermin was not associated with a lower risk of relapse of persistent epithelial defect or corneal ulcer, although patients treated with cenegermin had longer time to NK relapse compared to those treated with vehicle.

Based on the data available, it is unknown whether additional functional improvements could be achieved with longer or repeated courses of cenegermin therapy.

Harms Results

During the 8-week controlled treatment period of the NGF0212 and NGF0214 studies, the frequency of AEs was higher in the cenegermin group when compared with the vehicle group: 51.9% versus 38.5% in the NGF0212 trial; 91.3% versus 75.0% in the NGF0214 trial. Eye-related AEs were more commonly reported in both studies: 25.0% in the cenegermin group versus 30.8% in the vehicle group in study NGF0212; 78.3% in the antioxidant cenegermin group versus 58.3% in the antioxidant vehicle group in study NGF0214.

In the NGF0212 study, 9 patients (17.3%) in the cenegermin 20 mcg/mL group and 5 patients (9.6%) in the vehicle group experienced a serious adverse event (SAE), while in the NGF0214 study, 3 patients (13.0%) in the cenegermin 20 mcg/mL group and 4 patients (16.7%) in the vehicle group experienced an SAE. In the NGF0212 study, 9 patients (17.3%) in the cenegermin 20 mcg/mL group and 4 patients (7.7%) in the vehicle control group experienced AEs that led to discontinuation of study treatment, while in the NGF0214 study, 5 patients (21.7%) in the antioxidant cenegermin 20 mcg/mL group and 7 patients (29.2%) in the antioxidant vehicle group discontinued the treatment due to AEs. Disease progression, decreased visual acuity, and worsening of NK were the main reasons for SAEs and treatment discontinuation in these 2 studies.

One patient in the cenegermin group died during the controlled treatment period in study NGF0212. The death was not considered to be related to the study drug.

Sight-threatening AEs were considered as notable harms in the 2 studies. In the NGF0212 trial, notable harms were reported for 9 patients (17.3%) receiving cenegermin 20 mcg/mL and 5 patients (9.6%) receiving vehicle during the controlled treatment period; in the NGF0214 trial, notable harms were reported for 2 patients (8.7%) receiving cenegermin 20 mcg/mL and 3 patients (12.5%) receiving vehicle during the controlled treatment period.

Safety data were analyzed during various treatment periods (controlled, uncontrolled, and follow-up). Significant safety signals were not detected.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with moderate to severe NK who have failed conventional nonsurgical treatments
Treatment	Cenegermin
Submitted price	Cenegermin, 0.002% (20mcg/mL), ophthalmic solution: $2,111.25 per vial
Treatment cost	Full course of treatment (8 weeks; 56 days), 1 vial per day, costs $118,230
Comparators	• AMT • Surgical tarsorrhaphy

Component	Description
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (36 years)
Key data sources	Treatment efficacy of cenegermin from a pooled analysis of the NGF0212 (REPARO; Bonini et al. [2018]) and NGF0214 (Pflugfelde et al. [2019]) trials. Treatment efficacy of the surgical comparators (AMT and surgical tarsorrhaphy) from published literature and clinical expert input.
Key limitations	• There is limited comparative clinical evidence for cenegermin vs. current treatment alternatives, regarding corneal healing, deterioration, and recurrence. As there is no direct or indirect evidence for the clinical efficacy of cenegermin vs. surgical tarsorrhaphy, information on the comparative effects is based on an unadjusted naive comparison and clinical expert opinion. One observational study with a small sample size was used to derive estimates of clinical efficacy of cenegermin relative to AMT. • The sponsor assumes the disutility associated with surgical tarsorrhaphy to be a combination of unilateral blindness and disfigurement, for a total decrement of 0.21 applied for 1 year. CADTH considers this an overestimation of the disutility given both variability in the published literature and clinical variability in surgical tarsorrhaphy related to the amount of vision loss and disfiguration (e.g., differences between temporary and permanent procedures) described by the clinical experts engaged for this review. • The sponsor assumed that re-treatment with cenegermin would not take place if a patient had a recurrence; however, in the pivotal trial, re-treatment with cenegermin was permitted for patients who experienced sustained healing and then recurred. The CADTH clinical experts suggested that they would be inclined to re-treat with cenegermin if a patient had experienced improvement during their first treatment course and then deteriorated. Re-treatment was not explored by the sponsor and the impact on cost-effectiveness is unknown. • The sponsor assumed that there would be limited follow-up of patients who achieve sustained healing on any of the 3 comparators. The clinical experts suggested that these patients would require lifetime follow-up. • It is unclear how the utility values used in the model were derived. Specifically, it isn't clear whether the EMA or FDA definitions of corneal healing were used when eliciting patient preferences. Details of the pooled analysis of HRQoL results from the pivotal trials were not clearly documented.
CADTH reanalysis results	• To account for the key limitations, several changes were made to derive the CADTH base case: clinical efficacy was assumed to be the same for cenegermin and both surgical comparators; follow-up for patients who achieved sustained healing was extended over the lifetime time horizon; and, the disutility associated with surgical tarsorrhaphy was reduced to –0.14. • In the CADTH base case, cenegermin is dominated by AMT due to the lack of additional clinical benefit (i.e., both treatments provided the same number of QALYs, and AMT was $114,597 less expensive). When compared to surgical tarsorrhaphy, cenegermin had an ICER of $1,368,740 per QALY gained (additional QALYs = 0.09; additional costs = $115,898). • To achieve cost-effectiveness at a $50,000 per QALY threshold, a price reduction of 95% would be required. • A scenario analysis that further reduced the disutility associated with surgical tarsorrhaphy markedly increased the ICER of cenegermin vs. surgical tarsorrhaphy to $23,320,230 per QALY.

AMT = amniotic membrane transplant; EMA = European Medicines Agency; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LY = life-year; NK = neurotrophic keratitis; QALY = quality-adjusted life-year; vs. = versus.

Budget Impact

The CADTH reanalysis of the sponsor's budget impact analysis increased the market shares for cenegermin and increased the proportion of patients eligible for public coverage. In the CADTH base case, the budget impact is expected to be $5,911,500 in year 1; $17,498,040 in year 2; and $19,271,490 in year 3; with a 3-year total budget impact of $42,681,030.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: April 28, 2022

Regrets: None

Conflicts of interest: None