CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

cenegermin (Oxervate)

(Dompé Farmaceutici S.p.A)

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

June 9, 2022

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0704
Name of the drug and Indication(s)	Cenegermin (Oxervate) for the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) NK in adults
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification. The reason for reimbursement condition 2 could be interpreted as conflicting with a statement in the CADTH clinical report.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here. Implementation guidance for reimbursement condition 1 could be misinterpreted (revised text suggested). A description of what it means to “respond well” would be helpful. Implementation guidance for reimbursement condition 3 would be helpful, if possible.

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CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0704
Brand name (generic)	Cenegermin eye drops
Indication(s)	Neurotrophic Keratitis
Organization	Dompe
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

Dompé appreciates the time and the work done by CADTH in assessing Oxervate (cenegermin eye drops) for potential reimbursement by participating jurisdictions. However, the company disagrees with the draft recommendations below, based on (1) Scientific errors and misinterpretation of the data made during the assessment, (2) Procedural flaws and (3) Inappropriate economic constraints applied to a treatment for a rare disease.

The company notes the following scientific errors and misinterpretations of the data.

- **Condition 2:** *"Patients must not have had prior treatment with cenegermin (with or without treatment success)- There is no evidence to demonstrate whether patients would benefit from re-treatment with a subsequent course of cenegermin."*
    - The company has provided evidence to support retreatment for patients who have recurred following a single 8-week course with cenegermin. Recurrence is defined as the patients experiencing return to baseline of disease. In the NGF0214 study, two patients who were treated with cenegermin during the controlled treatment period achieved complete corneal healing, but had recurrence of disease during follow-up. Both patients achieved complete healing again after a second course of cenegermin in the study setting. In addition, three out of nine patients who were initially treated with vehicle and then treated with cenegermin during the uncontrolled treatment period and achieved complete healing, later had a recurrence, and were retreated with cenegermin. Of these patients, two out of three achieved complete healing. Together, these data from RCTs provide evidence demonstrating that patients can benefit from re-treatment.

- **Condition 3:** "*The maximum duration of authorization of cenegermin should be eight 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."*
    - There is substantial evidence to demonstrate that treatment with cenegermin is safe and well tolerated. There is not scientific rationale to presume that patients who have partially responded to treatment without full resolution of disease within 8 weeks would not benefit from an extension of therapy. In particular, Oxervate remains the final option and the only non-surgical treatment for many patients who have been refractory to unapproved therapies.

- **Condition 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."*
    - As a reason for this condition, CADTH notes that in clinical trials patients were required to discontinue all topical ophthalmic medications. However, CADTH's interpretation of the study design is being improperly used to justify a lack of concurrent treatment with other therapies that might be deemed appropriate by physicians. Clinical trials are designed to limit variability such that efficacy and safety effects of the investigational product can appropriately be evaluated. In fact, many therapies seeking marketing authorization design studies in this manner with the objective of obtaining approval by regulatory authorities. CADTH stated "no evidence was identified to demonstrate an additional benefit of cenegermin in conjunction with other topical ophthalmic treatments." This is a misinterpretation of why a concomitant medication would be needed. Cenegermin is intended to treat NK, while other topical medications could potentially be used to address co-morbidities. The concomitant use of ophthalmic treatments is highly case-dependent and is a decision best left to the treating physician.
    - This rationale above resulted in Health Canada's decision not to implement any restrictions on the approved cenegermin prescribing information.

Additional scientific objections are noted related to the Economic Evidence section of the CADTH report, specifically Table 3.

- The sponsor and CADTH agree that there is a lack of direct evidence to compare cenegermin with unapproved and off-label treatments, including surgery, for the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) NK in adult patients
    - Dompé produced the highest level of scientific evidence (called Tier 1 evidence) for cenegermin, which supported a breakthrough designation and approval by Health Canada. Well-controlled studies in diseases without treatment, like NK, are often designed to compare active ingredients to placebo or inactive ingredients. In fact, to our knowledge, no ophthalmic product has ever run a clinical trial against an unapproved treatment or a surgical procedure.
    - Clinical experts chosen by CADTH and stated in the clinical review report, cenegermin has a unique mechanism of action which may cure the disease instead of being used for symptom control. The experts provided clinical rationale for why the cenegermin results should not be assumed equal to comparators.
    - We strongly disagree with CADTH's holding that the company should compare cenegermin to unapproved treatments, either directly in a clinical setting, or through the indirect use of cross-trial comparisons.
- To establish efficacy of comparator therapies, CADTH extrapolated cenegermin's clinical efficacy and applied it to two surgical comparators which are not indicated for neurotrophic keratitis: amniotic membrane transplantation (AMT) and temporary or permanent closure of the eye (surgical tarsorrhaphy). It is inappropriate to assume that efficacy and safety of one treatment could be applied to another in the absence of a non-inferiority study, or in this case, in the absence of any Tier 1 evidence for the unapproved comparator treatments.

The company notes procedural flaws specifically related to the disregard of Real World Evidence (RWE) for cenegermin, contrary to its own RWE policies.

- CADTH's own guidance provides that real world evidence may be particularly important for rare conditions or innovative and breakthrough technologies, as there may be gaps in the information provided through clinical trials. RWE was submitted for cenegermin, including publications by Bruscolini and Mastropasqua. This RWE provided directional evidence about the long-term efficacy of cenegermin and its ability to impact the pathogenesis of the disease, but the data were discarded due to the small number of patients available for follow-up.
- In contrast, for unapproved comparator treatments that are not well-studied and where published data is meagre, CADTH applied a different standard, creating a product profile based on the impressions of a small group of advisors. This represents an inconsistent application of scientific standards and resulted in a health economic reanalysis and conclusion that inappropriately favors unapproved therapies based on limited clinical evidence. Furthermore, specification of input parameters should not be taken sparingly from previous literature, as they could cause estimation errors; excessive approximation can negatively affect the health of the population of interest.

Finally, the sponsor objects to inappropriate economic constraints applied.

- **Condition 6**: **"***A reduction in price"* CADTH notes the reasons for this recommendation being *"cenegermin is dominated by AMT due to lack of additional clinical benefit and it is associated with greater costs."*
    - The use of pharmacoeconomic modelling to evaluate the cost-effectiveness of drugs for rare diseases is rife with challenges and is especially inappropriate in this setting. A $50,000 per QALY threshold can prevent rare disease medicines from reaching patients who need them, as it makes the business unsustainable.
    - In the case specifically of cenegermin, the comparators used in CADTH's model are not approved therapies. Cenegermin is the only drug with a marketing authorization for NK supported by double-masked pivotal clinical studies, or by any Tier 1 evidence.
        - To establish efficacy of comparator therapies that inappropriately informed the economic model, CADTH extrapolated cenegermin's clinical efficacy and applied it to two unapproved surgical comparators: amniotic membrane transplantation (AMT) and temporary or permanent closure of the eye (surgical tarsorrhaphy). This is particularly erroneous since the mechanism of action of cenegermin targets the underlying pathology of NK, thus curing the disease for a significant portion of patients. Surgical approaches may in some cases preserve the anatomy of the eye by avoiding or patching a corneal perforation, but often they do not save the function of the eye (vision), they can be cosmetically unacceptable to patients, and they do not address in any way the underlying disease.
    - When considering disutility as a driver for the PE calculations, CADTH underestimated the harm to patients of having complete or total vision impairment in the affected eye resulting from eyelid closure and did not adequately consider the impact of facial disfigurement on patients. Both tarsorrhaphy and AMT may lead to considerable visual impairment and disfigurement that could otherwise be avoided with cenegermin eye drop therapy.
    - Dompé respectfully deems the comparison with surgical tarsorrhaphy and AMT highly inadequate.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
If not, what aspects are missing from the draft recommendation? **Please see comments in Section 1.**		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. **Please see comments in Section 1.**		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. **Please see comments in Section 1.**		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. **Please see comments in Section 1.**		

[a] CADTH may contact this person if comments require clarification.