CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

AVALGLUCOSIDASE ALFA (Nexviazyme)

(Sanofi Genzyme, a division of sanofi-aventis Canada Inc.)

Indication: For the long-term treatment of patients with late-onset Pompe disease (LOPD).

March 31, 2022

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0703-000
Brand name (generic)	Nexviazyme (avalglucosidase alfa)
Indication(s)	Pompe Disease
Organization	The Neuromuscular Disease Network for Canada (NMD4C) and other Pompe Disease-treating clinicians
Contact information[a]	Name: Dr. Hanns Lochmüller

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

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

Recognizing that avalglucosidase alfa is likely to become the new standard treatment in Pompe disease, limiting the use of avalglucosidase alfa to only treatment naïve patients is unduly restrictive.

In the draft recommendations, treatment experienced patients -- even patients declining on current treatment--would not be eligible for this new, superior treatment. Inadequate justification for these exclusions is given. Indeed, the available evidence supports use of avalglucosidase alfa in treatment-experienced patients. It seems CDEC was primarily concerned that the degree of efficacy of switching was not clear: *"However, CDEC also noted that there is substantial uncertainty in the presented data that CDEC is unable to determine the efficacy of switching compared to maintaining original therapy."* CDEC seems to be questioning the statistically significant non-inferiority of avalglucosidase alfa. Since CDEC foresees the use of avalglucosidase alfa to be **cost-saving** in comparison to alglucosidase alfa, CDEC recommending that patients *not be allowed to switch* is discordant with both the clinical and economic evidence.

This excessive over-restriction removes too much agency from patient-physician shared decision-making. CADTH/CDEC must be aware that a key limitation of their recommendations is the very limited ability for physicians and patients to request revised CADTH/CDEC recommendations as further experience and evidence build over the years. (Please see the relevant editorial by Bayoumi and Laupacis published in CMAJ recently, *"Outdated criteria for drug plan reimbursement obstruct evidence-based care."*[1] Therefore, we urge you to use a framework for reimbursement decision-making that allows the required flexibility for patient-specific treatment planning.

In our Clinician Input we advised that CDEC establish eligibility criteria for avalglucosidase alfa to include:

1. patients who do not tolerate alglucosidase alfa, or
2. patients whose disease progresses under treatment with alglucosidase alfa,
3. patients who exhibit lack of improvement on alglucosidase alfa

[1] https://www.cmaj.ca/content/193/40/E1573

We also posit one other switching criteria for consideration. Recall that in 2009 there was a global supply shortage of alglucosidase alfa due to demand for alglucosidase alfa outgrowing manufacturing capacity, as well as problems with the manufacture of the medicine at some sites. If such a shortage were to again occur,

4. it is critical that patients be given the opportunity to switch from a treatment that is no longer available to the (likely) new standard treatment in Pompe disease - avalglucosidase alfa.

Of the four categories stated above where we believe patients should have the opportunity to access avalglucosidase alfa, physicians that treat Pompe disease may concede that in the case of "*patients who exhibit lack of improvement on alglucosidase alfa*" (#3), that perhaps those patients have the least urgent requirement to have the opportunity to switch. Given the lack of a multitude of alternative disease modifying therapies, it is our strong opinion that patients who are declining on alglucosidase alfa should be given the opportunity to try avalglucosidase alfa as an alternative, rather than be left to decline without effective treatment.

Again, in recognition that CDEC foresees the use of avalglucosidase alfa to be cost saving in comparison to alglucosidase alfa, NMD4C (and other Pompe Disease-treating clinicians) do not see any reason to restrict access to this treatment to only treatment naïve patients.

We do note that CDEC anticipates the possible availability of a biosimilar of alglucosidase alfa sometime in the future and hypothesizes that avalglucosidase alfa may not be cost-effective vs a biosimilar of alglucosidase alfa should such a product enter the market. In response, we believe that basing a large part of a reimbursement recommendation on conjecture about a product that does not currently exist, and may not ever exist is imprudent and unduly speculative.

The contributing authors of this submission have a question for CDEC to consider:

> Does CDEC think that the clinical rationale for someday switching patients currently *intolerant of alglucosidase alfa, or whose disease progresses on alglucosidase alfa, or who exhibit lack of improvement on alglucosidase alfa,* to (a not yet developed) biosimilar of alglucosidase alfa is somehow stronger than the clinical rationale to switch patients currently on alglucosidase alfa to avalglucosidase alfa?

<u>Discontinuation</u>

In Table 1, Reimbursement Condition #4 (Discontinuation) it states that Treatment with avalglucosidase alfa must be discontinued if the patient develops any of the following: (see 4.1, 4.2 & 4.3). In the Reason column, specifically with respect to 4.2 (..patient develops) *"High degree of disease severity with minimum life expectancy"*, it states that *"This is aligned with the Canadian guidelines for the diagnosis and management of Pompe disease."* This is not true: the current 2016 Canadian guideline **in fact** recommends consideration of treating patients with severe disease to determine whether that particular patient experiences benefit on a case-by-case basis.

With respect to 4.1. it states that treatment must be discontinued if there are "*severe infusion-related reactions"*. If the patient also reacts to alglucosidase alfa, then stopping all treatment means the patient faces faster disease progression as there are no other treatment options. Therefore, some patients will request a de-sensitization protocol. After counselling on the risks and careful planning with an immunologist, a de-sensitization protocol could be reasonable (PMID: 27637292).

This current CADTH recommendation is therefore overly restrictive, and unreasonably limits patient options.

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	☒

No, the CADTH Reimbursement Recommendation seems to have not considered the expert input of Pompe disease-treating physicians. Our interpretation of the data is that it offers clinical evidence that *all patients with LOPD, and especially those under the age of 50 years (NEO1/NEO-EXT), could see improvement with avalglucosidase alfa over alglucosidase alfa related to prevention of deterioration of respiratory and motor function, and functional endurance, as well as improved safety and health-related quality of life.*

We assume also that the clinical expert consulted by CADTH agrees with NMD4C on the interpretation of the data as the reimbursement recommendation stated *"The clinician group input was similar to that given by the clinical expert."*

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.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

The definition of ambulation provided is too restrictive as it does not allow the use of walkers. One of the contributing physicians to this *feedback* reports that half of Pompe patients in her clinic use walkers for their safety. Asking a patient to risk a fall just to see if they can walk 40 meters unaided, and thereby qualify for their treatment, is ethically unacceptable and puts trating physicians at unnecessary medico-legal risk. The 6 min walk test allows the use of aids. COMET included patients with walkers. We advise CDEC to remain consistent with ambulation testing protocols used in clinical practice and to consider the safety of patients.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

While we believe CDEC has made significant errors in its assessment of the evidence, the reimbursement conditions and the (erroneous) rationale for the conditions are clearly stated.

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

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0703
Name of the drug and Indication(s)	Avalglucosidase alfa (Nexviazyme) for the long-term treatment of patients with late-onset Pompe disease (acid alpha-glucosidase deficiency)
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

b) Reimbursement conditions and related reasons

Can CDEC provide a definition of ‘late onset Pompe disease’? How is it differentiated from infantile onset Pompe Disease? It is unclear if it is differentiated by enzyme activity or age.
If it is possible that patients less than 3 years of age may be diagnosed with late onset Pompe disease, can CDEC provide some context for that population?
(Please see below discussion regarding the place in therapy for Myozyme and Nexviazyme for IOPD and LOPD).

In Section 4 – Discontinuation, can CDEC please clarify what is meant by ‘High degree of disease severity’? Should this align with the definition of ‘severe disease’ as defined in the implementation guidance in Section 2?
Can CDEC also further clarify how motor/respiratory function should be assessed (specific tools, scales)? There is no stated threshold for degree of decline in motor or respiratory function. How would the prescriber characterize the rate of decline prior to therapy? If the patient received prompt treatment, we may not have measurements demonstrating decline over time.

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 is requested for Reimbursement Condition 3 (regarding Renewal) listed in Table 1. It could either outline what constitutes an acceptable response to therapy to justify renewal or outline that funding should be withdrawn if patients meet any of the discontinuation criteria.

In the discussion points, the first statement compares clinical benefit of alglucosidase alfa (Myozyme) and avalglucosidase alfa (Nexviazyme), and the second statement discusses switching between the 2 products. Myozyme was previously reviewed by CDEC only for the indication of *infantile onset Pompe Disease*. These statements suggest that Myozyme may also be effective for treatment of *late onset Pompe Disease*. Can CDEC please clarify how the indications are differentiated and what the treatment options are for the different indications? Is there a need to reconsider Myozyme for the indication of late onset Pompe Disease?

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0703-000
Brand name (generic)	Nexviazyme (avalglucosidase alfa)
Indication(s)	Pompe Disease
Organization	Muscular Dystrophy Canada (MDC) Canadian Association of Pompe (CAP)
Contact information[a]	Name: Homira Osman (MDC) [redacted]

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

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

"Treatment with avalglucosidase alfa should be reimbursed when initiated in patients with all the following: 1.1. a confirmed diagnosis of late-onset Pompe disease, 1.2. 3 years of age and older, 1.3. ambulatory, 1.4. treatment naïve"

- The current set of recommendations limits the option to treatment naïve patients, thus restricting and unjustifiably limiting treatment options for patients that might benefit from avalglucosidase alfa.

"Ambulation is defined as the ability to ambulate more than 40 meters without stopping and without an assistive device in a clinical assessment setting."

- The current set of recommendations restricts avalglucosidase alfa to those who can ambulate more than 40 meters without an assistive device.
- Compared to the six-minute walk test (6MWT), which is familiar to patients affected by Pompe, this 'test' to assess ambulation is problematic. The 6MWT instructs patients to walk with any assistive device or orthotic they would use to walk for 6 minutes.
- As noted in the patient input submission, patients are eager/keen to receive treatment and if required based on the current recommendations, they will walk 40-meters unaided in order to be considered eligible. However, this eagerness to engage in the clinical test comes with risk, particularly for falls.
- Not allowing use of assistive devices (e.g., walkers) is far too restrictive.
- COMET included patients with walkers.
- Having the ability to walk at least 40 meters without the aid of an assistive device limits opportunities for other patients who are non-ambulatory to experience slowing down of progressive or maintaining ability and preventing serious secondary health conditions. This is important from a quality of life perspective, in addition to, the possibility of a decrease in utilization of health care and community resources.

"The evidence from the COMET trial supported the efficacy and safety of treatment with avalglucosidase alfa for patients with the outlined clinical criteria."

- Clinical trials in rare diseases are more challenging than clinical trials in more common diseases. In addition to small number of patients affected by a disease, patients may be in various stages of a disease and disease courses may be far from uniform – which is certainly the case with Pompe disease.
- The COMET Trial has imperfections (e.g., inclusion and exclusion criteria). Limiting participants to those who are treatment naïve or those who are ambulatory were deliberate so that researchers had a higher likelihood of discerning significant differences in a small population, but certainly do not speak to potential benefit.

- As the evidence from the COMET Trial is far too narrow, we ask the CDEC committee to consider other types of evidence i.e. international data, clinical outcomes, real-world evidence, patient input and clinical expert input.

"CDEC noted that there is substantial uncertainty in the presented data that CDEC is unable to determine the efficacy of switching compared to maintaining original therapy."

- We fully agree with clinicians who note that CDEC establish eligibility criteria for avalglucosidase alfa to include:
- patients who do not tolerate alglucosidase alfa, or
- patients whose disease progresses under treatment with alglucosidase alfa,
- patients who exhibit lack of improvement on alglucosidase alfa
- patients be given the opportunity to switch from a treatment that is no longer available to the (likely) new standard treatment in Pompe disease - avalglucosidase alfa.
- Our patient input submission strongly demonstrated that some patients that received alglucosidase alfa observed a "minimal (or plateau) effect."
- The current set of recommendations would restrict individuals who provided the following testimonials in the original patient input submission:
- *"I am a Myozyme patient with zero side effect. It worked really well in the beginning but I plateaued and I've been regressing since."*
- *"He has received ERT. We find that in the first few years, he was thriving but now he has plateaued. We don't see any improvements but also not much decline."*
- *"Myozyme is the only treatment that's been available in our area, it definitely slowed the down progression of his disease but the longer he was on it the more it affected his mental health. The only way to manage it was to stop the Myozyme."*
- Additionally, in the patient input submission it was clear that patients desire for a treatment that can slow down progression. We see no reason not to leave the decision about switching between the patient and their physician. Shared decision-making is vital.

"Using the sponsor submitted price for avalglucosidase alfa and publicly listed prices for all other drug costs, avalglucosidase alfa was less costly compared with alglucosidase alfa and considered similarly effective."

- Since CDEC foresees the use of avalglucosidase alfa to be cost-saving in comparison to alglucosidase alfa, CDEC recommending that patients not be allowed to switch conflicts with both the clinical and economic evidence.

"Treatment with avalglucosidase alfa must be discontinued if the patient develops any of the following: 4.1. Severe infusion-related reactions. 4.2. High degree of disease severity with minimum life expectancy. 4.3. Declining motor or respiratory function at a similar rate as prior to therapy to the point of loss of ambulation or the need for mechanical ventilation."

- It is critical that there is a pathway for patients living with a fatal rare disease (i.e., minimum life expectancy) to access treatments. Through patient submissions and other consultations, patients have expressed that patients should be afforded the opportunity to work with their neuromuscular specialist and make informed decisions about treatment options.

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?

No, the CADTH Reimbursement Recommendation seems to have not considered the rich, poignant, valued lived experience input of patients affected by Pompe disease. In fact, it appears the current set of recommendations is in contrast with the patient input provided. It is not clear whether the patient input submission or supplementary patient videos were taken into consideration by the Committee – which is problematic especially as the input

submission incorporates the perspectives and experiences of the majority of Canadians living with documented/known Pompe disease.

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.

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 above re: definition of ambulatory.

"It is possible that biosimilars of alglucosidase alfa will enter the market in the future, though at the time of this review, the comparative efficacy or cost effectiveness of such biosimilars versus avalglucosidase alfa is unknown. CDEC considered there to be a potential risk of avalglucosidase alfa not being cost effective versus a biosimilar of alglucosidase alfa should such a product enter the market."

- As biosimilars do not currently exist, this note appears invalid. Patients affected by Pompe disease currently do not have access to biosimilars.

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.

[a] CADTH may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by CADTH.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Homira Osman*
Position	*Vice-President, Research & Public Policy*
Date	*30-03-2022*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it. Please note, we worked together to gather feedback from the Canadian Association of Pompe and to ensure this response reflects their position/perspectives on the current set of recommendations.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

sanofi

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0703
Brand name (generic)	NEXVIAZYME™ (avalglucosidase alfa for injection)
Indication(s)	NEXVIAZYME™ (avalglucosidase alfa for injection) is an enzyme replacement therapy (ERT) indicated for the long-term treatment of patients with late-onset Pompe disease (LOPD) (acid α-glucosidase deficiency).
Organization	Sanofi Genzyme, a division of sanofi-aventis Canada Inc.
Contact information	[redacted]

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

Partial agreement. Sanofi agrees with the Canadian Drug Expert Committee's (CDEC) recommendation to reimburse NEXVIAZYME™ (avalglucosidase alfa for injection) for the long-term treatment of naïve patients with LOPD but requests further details on the exclusion of enzyme replacement therapy (ERT)-experienced patients.

Pompe disease is a rare, inherited, progressive, and degenerative disorder which when left untreated can be fatal. As stated by CADTH clinician expert (Draft CRR pg. 9)[1], the main goals of treatment for Pompe disease are "*…to stabilize and/or improve motor and respiratory function as well as prevent further disease progression. New treatments should have improved immune tolerance, low risk of treatment related reactions, and less burden on patients …*" Alglucosidase alfa (ALGLU) was the first approved ERT and has been the standard of care in the treatment of patients with Pompe disease for decades. Although ALGLU has changed the natural course of Pompe disease, an unmet need exists for a therapy that can further sustain improvement and stabilize the disease over the long-term. Avalglucosidase alfa (AVA) was specifically designed to overcome the limitations of ALGLU and to enhance receptor targeting and enzyme uptake into muscle cells in patients with Pompe disease. By increasing cellular uptake, AVA provides enhanced degradation of lysosomal glycogen and prevention of accumulation and tissue damage.

Sanofi agrees that the evidence reviewed by CDEC supports the recommendation for patients with LOPD that are treatment naïve. However, Sanofi is seeking additional clarity regarding CDEC's rationale for not including reimbursement for ERT-experienced patients: "*CDEC recommended that treatment with AVA should not be reimbursed when initiated in patients who previously received ALGLU.*" (Draft reco, pg. 8) This is especially in consideration of Table 2 (pg. 8), the question from the drug programs was "*Should patients unresponsive to ALGLU be considered for AVA therapy?*" and CADTH's "*clinical expert consulted suggested that patients may respond when switched from ALGLU to AVA*".

Sanofi is seeking clarification on why CDEC did not consider ERT switch patients (including ALGLU responders), given the mechanism of action of AVA and the available switch data:

- COMET Extension (97 weeks)[2] - Of the 49 patients initially randomized to ALGLU, 44 entered the extended treatment period and were switched to AVA and reported stability or numerical improvement in outcomes.
- NEO-1 trial (Group 2)[3] - Data supports disease stabilization in patients previously treated with ALGLU and received AVA over the duration of the trial
- NEO-EXT[4] – Data for up to 6 years supports continued disease stabilization in patients previously treated with ALGLU.

Of note: Health Canada reviewed the same data and concluded that AVA was associated with a favorable benefit/risk profile for the long-term treatment of all patients with LOPD (i.e., with no differentiation between treatment naïve and ERT-experienced patients).

NEXVIAZYME™ represents a next generation ERT that can facilitate improvement and/or stabilize respiratory and motor functions over the long-term. There is an important unmet need for a new ERT with sustainable efficacy and increased enzyme delivery, especially to respiratory muscles, as such, **Sanofi *requests further clarification be added that acknowledges the cumulative evidence available for switch patients.***

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	☒

While Sanofi agrees that the CDEC recommendation considered the stakeholder input when it comes to the recommendation for treatment naïve patients, the recommendation does not consider the stakeholder input in support of the ERT-experienced patients.

The recommendation states that *"there is no evidence to suggest that switching patients to AVA provides any clinical benefit over maintaining therapy with ALGLU*" (Draft reco, pg. 5 and Table 2, pg. 8) and that "*there is no evidence to suggest that patients who are not responding well or experience a plateaued response on ALGLU would benefit from switching to AVA* (Draft reco, pg. 5).

- Sanofi input: As indicated above in section 1, clinical evidence on switch data have been provided and showed that the stability in respiratory function, motor function, muscle strength, and health-related quality of life was maintained and no safety- or immunogenicity-related concerns has been raised. Moreover, efficacy and safety results after 97 weeks from the extended treatment period (ETP) of participants who received ALGLU in the primary analysis period (PAP) and switched to AVA (n=44) are now available and published (COMET extension data).[2] **Therefore, Sanofi respectfully requests that statements on "no evidence" be updated to reflect the evidence provided by the manufacturer.**

The access of NEXVIAZYME™ as per the Health Canada indication has been expressed by other stakeholders:

- Patient input stated: "*Patients and caregivers would like for new treatments to improve strength, breathing function, and prevent disease progression.*" (Draft reco, pg. 6)
- Clinician group input stated: "AVA *would likely become the standard of care first-line therapy, replacing ALGLU, for the treatment of all patients with LOPD"* (Draft CRR pg. 23)[1] "*For LOPD all the data in adults shows AVA is at least as efficacious and likely a better treatment than ALGLU.*" (Draft CRR pg. 87)[1]
- CADTH clinical expert expected the place in therapy for AVA as follows: "*that AVA would replace ALGLU as first-line treatment for Pompe disease and all patients who meet the criteria for treatment would receive the new drug. This would include those who have never received enzyme replacement therapy as well as those already being treated with ALGLU who would be switched over to AVA.*" (Draft reco, pg. 7) "*The clinical expert also noted that there may be situations in which patients can be reviewed on a case-by-case basis"*(Draft CRR, pg. 25)[1]. The CADTH clinical expert also indicated that *"data are available from COMET trial for patients who received ALGLU for 1*

year and switched to AVA." (Draft CRR, pg. 25)[1] . **Sanofi respectfully requests that the CADTH clinical expert perspective be reflected in the discussion points of the recommendation if considered by CDEC.**

- Drug Plan input: They asked the question "*if data are available regarding switching?" (*Draft reco, pg. 8) *"CDEC noted that data exist…however CDEC also noted that there is substantial uncertainty in the presented data that CDEC is unable to determine the efficacy of switching compared to maintaining original therapy*." CADTH acknowledged that clinical evidence is available but did not describe what they included in that assessment or how they concluded there was uncertainty. Further clarification is needed.
- Drug Plan input: They asked the question *"if prescribing criteria for AVA be aligned with the prescribing criteria for ALGLU*?" The CADTH clinical expert' response was: *"Prescribing criteria for AVA should be aligned with that for ALGLU and for LOPD rather than IOPD"* which means for the full LOPD population to facilitate the implementation of reimbursement criteria.

In conclusion, the recommendation does not fully consider the evidence provided by Sanofi, nor the input from patients and clinician group, CADTH's clinical expert, and drug programs. ***Based on stakeholder input, Sanofi respectfully requests acknowledgement that patients can be safely switched.***

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

Partially clear, as noted above Sanofi does not believe the reasons clearly articulate why ERT-experienced patients are excluded from the reimbursement given the submitted evidence.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

Although most implementation issues have been clearly articulated, it is unclear why the recommendation includes a statement about biosimilar products: "*It is possible that biosimilars of ALGLU will enter the market in the future, though at the time of this review, the comparative efficacy or cost effectiveness of such biosimilars versus AVA is unknow* (Draft reco, pg. 5). To date, there is no ALGLU biosimilar approved in Canada nor is there currently a biosimilar seeking approval through Health Canada. Any statements pertaining to biosimilar are speculative and do not belong in an evidence-based recommendation. ***Sanofi respectfully requests that this statement be removed.*** The economic evidence submitted by Sanofi demonstrated a cost-savings versus ALGLU.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

The first Reimbursement Condition stipulates the "*treatment with AVA should be reimbursed when initiated in patients" who are treatment naïve* (Draft reco, Table 1, pg. 4) with the reason that "*evidence from the COMET trial supported efficacy and safety of treatment*" with AVA in this patient population. Sanofi believes this condition ignores the input from the clinical expert consulted by CADTH who "*expected that AVA would replace ALGLU as first-line treatment for Pompe disease and all patients who meet the criteria for treatment would receive the new drug"*. Sanofi believes restricting the reimbursement conditions to the treatment naïve population places significant limitations and burden on patients and prescribers and, therefore, **requests that further clarity and rationale for the disconnect between the clinical expert and the reimbursement recommendation be provided in the recommendation as Sanofi believed that the choice of ERT should be based on patient characteristics, objectives of treatment, and clinical judgement of the prescriber.**

REFERENCES

1) CADTH Reimbursement Review Clinical Review Report – Avalglucosidase alfa (Nexviazyme) – Draft report – February 10, 2022 (CONFIDENTIAL)
2) Kishnani PS et all, The avalglucosidase alfa phase 3 COMET trial in Late-Onset Pompe Disease Patients: efficacy and safety results after 97 weeks. ePoster presented at the 18th WORLD Symposium, San Diego CA, USA Feb 17-11, 2022. https://www.sciencedirect.com/science/article/pii/S1096719221009860
3) Pena LDM, Barohn RJ, Byrne BJ, et al. Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study. Neuromuscular disorders: NMD 2019; 29:167-86.
4) Schoser B, Barohn RJ, Byrne B, et al. NEO1/NEO-EXT studies: Safety and exploratory efficacy of repeat avalglucosidase alfa dosing for up to 6 years in late-onset Pompe disease (LOPD) [poster P.03]. The 25th International Annual Virtual Congress of the World Muscle Society 2020.

CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

AVALGLUCOSIDASE ALFA (Nexviazyme)

(Sanofi Genzyme, a division of sanofi-aventis Canada Inc.)

Indication: For the long-term treatment of patients with late-onset Pompe disease (LOPD).

April 8, 2022

sanofi

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0703
Brand name (generic)	NEXVIAZYME™ (avalglucosidase alfa for injection)
Indication(s)	NEXVIAZYME™ (avalglucosidase alfa for injection) is an enzyme replacement therapy (ERT) indicated for the long-term treatment of patients with late-onset Pompe disease (LOPD) (acid α-glucosidase deficiency).
Organization	Sanofi Genzyme, a division of sanofi-aventis Canada Inc.
Contact information	[redacted]

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation?	Yes	☐
	No	☒

Sanofi agrees with the Canadian Drug Expert Committee's (CDEC) recommendation to reimburse NEXVIAZYME™ (avalglucosidase alfa for injection) for the long-term treatment of naïve patients with LOPD but disagrees with the exclusion of enzyme replacement therapy (ERT)-experienced patients.

Pompe disease is a rare, inherited, progressive, and degenerative disorder which when left untreated can be fatal. As stated by CADTH's clinician expert (Draft CRR pg. 9)[1], the main goals of treatment for Pompe disease are "…***to stabilize and/or improve motor and respiratory function as well as prevent further disease progression***. *New treatments should have improved immune tolerance, low risk of treatment related reactions, and less burden on patients.*" Alglucosidase alfa (ALGLU) was the first approved ERT and has been the standard of care in the treatment of patients with Pompe disease for decades. Although ALGLU has changed the natural course of Pompe disease, an unmet need exists for a therapy that can further sustain improvement and stabilize the disease over the long-term. Avalglucosidase alfa (AVA) was specifically designed to overcome the limitations of ALGLU and to enhance receptor targeting and enzyme uptake into muscle cells in patients with Pompe disease. By increasing cellular uptake, AVA provides enhanced degradation of lysosomal glycogen and prevention of accumulation and tissue damage.

Sanofi agrees that the evidence reviewed by CDEC supports the recommendation for patients with LOPD that are treatment naïve. However, Sanofi is seeking additional clarity on the committee's rationale to preclude reimbursement for ERT-experienced patients: "*CDEC recommended that treatment with AVA should not be reimbursed when initiated in patients who previously received ALGLU,"* (Draft reco, pg. 8) especially in light of the feedback provided by CADTH's clinical expert who "*suggested that patients may respond when switched from ALGLU to AVA"* (Draft reco, Table 2, pg.8)

Additionally, Sanofi would like to bring attention to the need to consider ERT switch patients (including ALGLU responders), given the mechanism of action of AVA and the available switch data:

- COMET Extension (97 weeks)[2] - Of the 49 patients initially randomized to ALGLU, 44 entered the extended treatment period, were switched to AVA, and reported stability or numerical improvement in outcomes.
- NEO-1 trial (Group 2)[3] - Data supports disease stabilization in patients previously treated with ALGLU and received AVA over the duration of the trial.

- NEO-EXT[4] – Data for up to 6 years supports continued disease stabilization in patients previously treated with ALGLU.

Of note: Health Canada's review of the data concluded that AVA was associated with a favorable benefit/risk profile for the long-term treatment of all patients with LOPD (i.e., with no differentiation between treatment naïve and ERT-experienced patients).

NEXVIAZYME™ represents a next generation ERT that can facilitate improvement and/or stabilize respiratory and motor functions over the long-term. There is an important unmet need for a new ERT with sustainable efficacy and increased enzyme delivery, especially to respiratory muscles, as such, **Sanofi respectfully requests that CADTH considers expanding the initiation criteria to include ERT-experienced patients, acknowledging the cumulative evidence available for switch patients.**

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	☒

While Sanofi agrees that the CDEC recommendation considered the stakeholder input when it comes to the recommendation for treatment naïve patients, the recommendation needs to incorporate the stakeholder input in support of the ERT-experienced patients.

The recommendation states that *"there is no evidence to suggest that switching patients to AVA provides any clinical benefit over maintaining therapy with ALGLU*" (Draft reco, pg. 5 and Table 2, pg. 8) and that "*there is no evidence to suggest that patients who are not responding well or experience a plateaued response on ALGLU would benefit from switching to AVA* (Draft reco, pg. 5).

- Sanofi input: As indicated above in section 1, clinical evidence on switch data have been provided and showed that the stability in respiratory function, motor function, muscle strength, and health-related quality of life was maintained and no safety- or immunogenicity-related concerns have been raised. Moreover, efficacy and safety results after 97 weeks from the extended treatment period (ETP) of participants who received ALGLU in the primary analysis period (PAP) and switched to AVA (n=44) are now available and published (COMET extension data).[2] **Therefore, Sanofi respectfully requests that statements on "no evidence" be updated to reflect the evidence provided by the manufacturer.**

Support for access to NEXVIAZYME™ as per the Health Canada indication has been expressed by other stakeholders:

- Patient input stated: "*Patients and caregivers would like for new treatments to improve strength, breathing function, and prevent disease progression.*" (Draft reco, pg. 6)
- Clinician group input stated: "AVA *would likely become the standard of care first-line therapy, replacing ALGLU, for the treatment of all patients with LOPD"* (Draft CRR, pg. 23)[1] "*For LOPD all the data in adults shows AVA is at least as efficacious and likely a better treatment than ALGLU.*" (Draft CRR, pg. 87)[1]
- CADTH clinical expert expected the place in therapy for AVA as follows: "*that AVA would replace ALGLU as first-line treatment for Pompe disease and all patients who meet the criteria for treatment would receive the new drug. This would include those who have never received enzyme replacement therapy as well as those already being treated with ALGLU who would be switched over to AVA.*" (Draft reco, pg. 7) "*The clinical expert also noted that there may be situations in which patients can be reviewed on a case-by-case basis"* (Draft CRR, pg. 25)[1]. The CADTH clinical expert also indicated that *"data are available from COMET trial for patients who received ALGLU for 1 year and switched to AVA."* (Draft CRR, pg. 25).[1] **Sanofi respectfully requests that the CADTH clinical expert perspective be reflected in the discussion points of the recommendation if considered by CDEC.**

- Drug Plan input: They asked the question "*if data are available regarding switching?" (*Draft reco, pg. 8) *"CDEC noted that data exist…however CDEC also noted that there is substantial uncertainty in the presented data that CDEC is unable to determine the efficacy of switching compared to maintaining original therapy*." CADTH acknowledged that clinical evidence is available but did not describe what they included in that assessment or how they concluded there was uncertainty. Further clarification is needed.
- Drug Plan input: They asked the question *"if prescribing criteria for AVA be aligned with the prescribing criteria for ALGLU*?" CDEC's response was: *"Prescribing criteria for AVA should be aligned with that for ALGLU and for LOPD rather than IOPD"* which suggests the full LOPD population to facilitate the implementation of reimbursement criteria.

In conclusion, the recommendation does not fully consider the evidence for ERT-experienced patients provided by Sanofi and needs to incorporate the input from the patient and clinician groups, CADTH's clinical expert, and drug programs. ***Based on stakeholder input, Sanofi respectfully requests acknowledgement that patients can be safely switched.***

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

Partially clear, as noted above Sanofi does not believe the reasons clearly articulate why ERT-experienced patients are excluded from the reimbursement given the submitted evidence.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

Although most implementation issues have been clearly articulated, it is unclear why the recommendation includes a statement about biosimilar products: "*It is possible that biosimilars of ALGLU will enter the market in the future, though at the time of this review, the comparative efficacy or cost effectiveness of such biosimilars versus AVA is unknow* (Draft reco, pg. 5). To date, there is no ALGLU biosimilar approved in Canada nor is there currently a biosimilar seeking approval through Health Canada. Any statements pertaining to biosimilar are speculative and do not belong in an evidence-based recommendation. ***Sanofi respectfully requests that this statement be removed.*** The economic evidence submitted by Sanofi demonstrated a cost-savings versus ALGLU.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

Although the reimbursement criteria do reflect the value of avalglucosidase alfa in the naïve patient population, they fail to acknowledge the value of avalglucosidase alfa in patients that may benefit from switching therapy.

The first reimbursement condition stipulates that the "*treatment with AVA should be reimbursed when initiated in patients [who are] treatment naïve"* (Draft reco, Table 1, pg. 4) with the reason that "*evidence from the COMET trial supported efficacy and safety of treatment*" with AVA in this patient population. Sanofi believes this condition ignores the input from the clinical expert consulted by CADTH who "*expected that AVA would replace ALGLU as first-line treatment for Pompe disease and all patients who meet the criteria for treatment would receive the new drug"*. Avalglucosidase alfa offers previously treated patients a therapeutic option in absence of a clinically effective drug or non-drug alternative. Sanofi believes restricting the criteria to the naïve population will place significant limitations and burden on patients and prescribers and believes that the choice of ERT should be based on patient characteristics, objectives of treatment, and the clinical judgement of the prescriber. As a result, **Sanofi respectfully requests that the implementation guidance be updated to reflect that the clinical context of the treatment of specific subpopulations be based on clinical judgement (i.e., case-by-case) of the prescriber.**

REFERENCES

1) CADTH Reimbursement Review Clinical Review Report – Avalglucosidase alfa (Nexviazyme) – Draft report – February 10, 2022 (CONFIDENTIAL)
2) Kishnani PS et all, The avalglucosidase alfa phase 3 COMET trial in Late-Onset Pompe Disease Patients: efficacy and safety results after 97 weeks. ePoster presented at the 18th WORLD Symposium, San Diego CA, USA Feb 17-11, 2022. https://www.sciencedirect.com/science/article/pii/S1096719221009860
3) Pena LDM, Barohn RJ, Byrne BJ, et al. Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study. Neuromuscular disorders: NMD 2019; 29:167-86.
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