CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

LUMASIRAN (Oxlumo)

(Alnylam Netherlands B.V.)

Indication: For the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients.

November 3, 2022

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0734
Name of the drug and Indication(s)	Lumasiran (Oxlumo) for primary hyperoxaluria type 1 to lower urinary oxalate levels in pediatric and adult patients.
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.
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. Initiation criteria: guidance for situations when urinary oxalate cannot be measured. Discontinuation criteria: guidance for pediatric populations where 24 hour urine oxalate cannot be measured. If patients progress to dialysis despite treatment, should this be considered a lack of response?

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CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0734
Brand name (generic)	Oxlumo (Lumasiran)
Indication(s)	Primary hyperoxaluria type 1
Organization	The Oxalosis and Hyperoxaluria Foundation
Contact information[a]	Name: Kim Hollander

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	X☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		

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?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	X
	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	X
	No	☐
If not, please provide details regarding the information that requires clarification.		
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. Responses were collected by The Oxalosis and Hyperoxaluria Foundation (The OHF) from those affected by primary hyperoxaluria type 1 (PH1) in Canada who have experience with Lumasiran (Oxlumo), coupled with the assessment of leading medical experts in primary hyperoxaluria. Feedback was provided and is numbered in accordance with *Table 1. Reimbursement Conditions and Reasons*.		

1. While it is acknowledged that genetic testing is key prior to beginning Lumasiran, families voice the importance of starting B6 prior to genetic diagnosis and *quickly* achieving a diagnosis if PH1 is suspected to enable the most effective treatment including Lumasiran to save kidney function and improve quality of life.

Moreover, experts in the field emphasize “Patients could/should be started on B6 pending the genetics if **PH1 is at all possible. [It is cost effective] and safe**. This has been very standard in practice to date.”

Experts further emphasized the importance of taking rapid action to achieve a diagnosis to make appropriate treatment possible “It should be feasible to get genetic [testing] done within 1-2 months with current companies and pipelines.”

Providers stressed this importance, particularly in young individuals and those with rapidly declining kidney function, “They should minimize the barriers to starting Lumasiran in children **under a year of age** and/or those with **evidence of rapidly declining GFR (kidney function),** as these patients likely have very aggressive disease. Anecdotally, **waiting 3-6 months in an infant could very well be the difference between progressing to end-stage kidney disease [and death] or not.** The proper management of an infant suspected of having PH is **rapid genetic testing and optimizing management which, in PH1, includes Lumasiran** in an effort to **save the kidney and avoid dialysis/transplant**.”

2. A family member raised questions about why B6 and time frame are initiation criteria if only a subset are responsive to this therapy, and this would be known through genetic testing. They also noted that some patients are partial responders. Further, this individual raised that Lumasiran may mitigate nephrocalcinosis in some, and B6 does not help with that.

“With the lengthy time frame to get a genetic test back and then **waiting the timeline to be on B6 it would be a huge loss to the patient for care**. In [my daughter’s] case she waited 6 months to get genetic testing back and wasn't even offered the option for B6 till then.”

Moreover, one expert raised “There is no provision for patients who…normalize their urine oxalate with B6, but **continue to form stones or who despite normal excretion show a progressive loss of renal function. These patients need to be included**.”

A family member raised the importance of **plasma oxalate** as an indication and suggested that it be added. An expert reinforced this stating, “an elevated plasma oxalate should be an indication” and suggested while **supersaturation is considered to be 30-50, levels of 10-15 are also important to consider**.

4. One expert disagreed with the definition of response being < 1.5 x ULN stating “If there is a **high body burden of oxalate, excretion may be reduced, but not to that level**. We define [B6] sensitivity as a 30% reduction in oxalate excretion. This 1.5 x ULN does not take into account people with a substantial drop who do not meet that criteria.” They also noted that it is not clear “if they are expecting this to happen in 6 months.”

6. One family member asked, “**What about adult patients**”? An expert raised the importance of including “ adult internists or possibly family physicians in partnership with a nephrologist or metabolic specialist for adult patients” to **ensure accessibility for adult patients**.

7. A family member highlighted that **drug to dialysis cost, surgical costs, emotional impact, and quality of life were not taken into consideration** for the drug-to-drug comparison made.

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

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	*Kim Hollander*
Position	*Executive Director*
Date	*11/07/2022*
x	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.		
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 or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0734
Brand name (generic)	lumasiran
Indication(s)	OXLUMO (lumasiran) is indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients.
Organization	Alnylam Pharmaceuticals Canada ULC
Contact information[a]	[redacted]

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

Alnylam request an edit to the following implementation guidance: "The clinical experts noted to CDEC that an increase in plasma oxalate or an increase in urine oxalate after an initial improvement would be considered as loss of response." We kindly request that the wording be updated to the following: "The clinical experts noted to CDEC that a sustained increase in plasma oxalate or a sustained increase in urine oxalate to pre-treatment baseline, after an initial improvement, would be considered as loss of response." We request this change as measurements in plasma and urinary oxalate can vary from measurement to measurement based on several factors unrelated to the efficacy of treatment (e.g. consumption of food), which is referred to as "normal intra-individual variation in oxaluria". As such, a single increase in either measure does not necessarily substantiate a loss of response. We therefore believe it is appropriate to clarify that a sustained increase, back to pre-treatment baseline, be considered a loss of response.

Additionally, we request an edit to the following implementation guidance: "The clinical experts noted to CDEC that for patients with ESKD or on dialysis, a 15% reduction in plasma oxalate levels after 1 year of treatment is considered as response." We kindly request that the wording be updated to the following: "The clinical experts noted to CDEC that for patients with ESKD or on dialysis, a 15% reduction in plasma oxalate levels after 2 years of treatment is considered as response." In the CADTH draft recommendation, the clinical experts noted that "substantial systemic oxalate burden may require years to normalize urinary excretion since the body is slowly clearing stored oxalate". We note that this statement from the draft recommendation is consistent with published literature which shows that plasma oxalate levels may take years to change due to the slow clearing of stored oxalate in these patients. Therefore, a 1-year time frame is not appropriate for verifying clearance of systemic oxalosis and assessing reduction in plasma oxalate, given that oxalate stores in the tissues may still be diffusing into the circulation leading to elevations in plasma oxalate even when hepatic oxalate production is effectively inhibited by lumasiran. To halt treatment at this stage could mean inappropriately stopping effective treatment for patients with no therapeutic alternatives.

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?

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.		
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.