CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

burosumab (Crysvita)

(Kyowa Kirin Canada, Inc.)

Indication: For the treatment of X-linked hypophosphataemia (XLH) in adult patients.

June 27, 2024

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0818-000
Brand name (generic)	Burosumab
Indication(s)	X-linked Hypophosphatemia (XLH)
Organization	Canadian XLH Network
Contact information[a]	Name: Shari Van Vugt

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.		

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.

The Canadian XLH Network is happy to see burosumab being supported for use in adult patients. From experience speaking to people with XLH, we have seen how much of an improvement the drug can have on a person's well being and quality of life, improving pain and stiffness. We have a couple of comments which we believe do not align with the current practices for the treatment of XLH and one that will make access to burosumab challenging for people who do not have funds to spend on testing.

1. "Burosumab must be prescribed by and endocrinologist or **rheumatologist…**" – While a person with XLH should be followed by a multidisciplinary team that may include a rheumatologist, in almost all cases from our experience this team is lead by an endocrinologist or a nephrologist, not a rheumatologist. This is supported by published clinical practice guidelines. Guidelines recommend patients to be followed by a multidisciplinary team lead by a metabolic bone disease expert, normally

recommended to be a nephrologist or endocrinologist.[1–5] Many people with XLH are being followed by someone with metabolic bone disease experience, that may not be an endocrinologist or rheumatologist, this leaves them possibly waiting months to see a new specialist to gain access to burosumab. Second, people living in rural areas may not have access to either an endocrinologist or rheumatologist, meaning they would not have access to burosumab. We believe limiting who can prescribe burosumab could completely block or delay care to people who do not have the same access to the outlined specialists.

2. Diagnosis must be supported by Serum intact FGF23 – We believe that this is overbearing and could block access to care for people who are less fortunate. In Ontario the FGF23 test is not accessible, the blood test must be sent out of country meaning that in most cases the patient will have to pay the cost to ship the sample, which can cost upwards of $400. This means that people who cannot afford this payment will be cut off from access to burosumab. In many clinical guidelines FGF23 is seen optional measurement to support diagnosis but it is not required, thus we believe it should not be required for an individual to gain access to burosumab in Canada, especially because the test is not widely accessible.[1,3,4,6]

References

1. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat Rev Nephrol*. 2019;15(7):435-455. doi:10.1038/s41581-019-0152-5

2. Sandy JL, Simm PJ, Biggin A, et al. Clinical practice guidelines for paediatric X-linked hypophosphataemia in the era of burosumab. *J Paediatr Child Health*. 2022;58(5):762-768. doi:10.1111/jpc.15976

3. Munns CF, Yoo HW, Jalaludin MY, et al. Asia-Pacific Consensus Recommendations on X-Linked Hypophosphatemia: Diagnosis, Multidisciplinary Management, and Transition From Pediatric to Adult Care. *JBMR Plus*. 2023;7(6):e10744. doi:10.1002/jbm4.10744

4. Laurent MR, De Schepper J, Trouet D, et al. Consensus Recommendations for the Diagnosis and Management of X-Linked Hypophosphatemia in Belgium. *Front Endocrinol*. 2021;12:641543. doi:10.3389/fendo.2021.641543

5. Al Juraibah F, Al Amiri E, Al Dubayee M, et al. Diagnosis and management of X-linked hypophosphatemia in children and adolescent in the Gulf Cooperation Council countries. *Arch Osteoporos*. 2021;16(1):52. doi:10.1007/s11657-021-00879-9

6. González-Lamuño D, Lorente Rodríguez A, Luis Yanes MI, Marín-del Barrio S, Martínez Díaz-Guerra G, Peris P. Clinical practice recommendations for the diagnosis and treatment of X-linked hypophosphatemia: A consensus based on the ADAPTE method. *Med Clínica Engl Ed*. 2022;159(3):152.e1-152.e12. doi:10.1016/j.medcle.2021.07.026

[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	Shari Van Vugt
Position	President/Chair
Date	26/06/2024
☒	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 company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Burosumab
Indication(s)	XLH
Organization	Adult Metabolic Diseases Clinic, Vancouver General Hospital
Contact information[a]	Name: Dr. Anna Lehman

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. Reimbursement condition #2: No convincing rationale was provided for deviating from the CL303 trial criteria for diagnosis of **either** PHEX mutation OR elevated FGF23, in the setting of a consistent clinical phenotype. It is not usually necessary to have **both** PHEX and FGF23 levels for making a diagnosis. Many places in Canada do not have ready access to FGF23 testing. Reimbursement condition #9: It is not necessary to restrict prescribing to endocrinologists and rheumatologists. There are a number of nephrologists and medical geneticists in Canada with special interest, training, and experience in metabolic bone diseases. Instead, it would be enough to require a physician trained and experienced in metabolic disease for the prescribing of burosumab---which would be consistent wording with the pediatric CADTH recommendation.		

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? N/A		

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.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it. We were contacted by Kiowa Kirin but we did not work with them in preparing this submission.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Anna Lehman*
Position	*Medical Director, Adult Metabolic Diseases Clinic*
Date	*Please add the date form was completed (27-06-2024)*
☒	**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**
Ultragenyx in 2022 and 2023	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Dr. Gabriella Horvath*
Position	*Metabolic Geneticist*
Date	*Please add the date form was completed (27-06-2024)*
☒	**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**
None	☐	☐	☐	☐
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	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0818
Brand name (generic)	Burosumab (Crysvita)
Indication(s)	For the treatment of X-linked hypophosphataemia (XLH) in adult and pediatric patients 6 months of age and older
Organization	CHU Sainte Justine
Contact information[a]	Melissa Fiscaletti

Stakeholder agreement with the draft recommendation

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

Thank you for the opportunity to provide feedback in support of reimbursement of Burosumab for adults with XLH. The CADTH recommendation represents a very positive step forward for patients with XLH. However, two recommendations will likely complicate implementation and will create barriers for patients, physicians, and allied-health professionals.

1. Page 4, Table 1, Point #2 of the draft recommendation:

> *"Diagnosis of XLH supported by classic clinical features of adult XLH (such as short stature or bowed legs) and **both** of the following:*
> *a confirmed PHEX gene variant in either the patient or a directly related family member with appropriate X-linked inheritance*
> ***AND***
> *Serum intact FGF23 (iFGF23) level > 30 pg/mL by Kainos assay"*

2. Page 5, Table 1, Point #9 of the draft recommendation:

> *"Burosumab must only be prescribed by an endocrinologist or rheumatologist with experience in the diagnosis and management of XLH."*

Further elaboration on these two points can be found below.

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	☐

Yes, but not completely.

Addressing the first point:
The requirement for confirmation with both genetic testing and intact FGF23 testing for a diagnosis of XLH creates logistic barriers, complicates the diagnostic algorithm, and potentially delays time to treatment.

The eligibility criteria in the CL303 (Insogna et al., 2018) required that patients enrolled in the study were diagnosed with a confirmed PHEX gene variant in either the patient or a directly related family member with appropriate X-linked inheritance **OR** a serum intact FGF23 (iFGF23) level > 30 pg/mL by Kainos assay, not both.

A positive PHEX finding of Pathogenic or Likely Pathogenic is diagnostic which indicates that a mutation of this gene is fully penetrant, and the individual-**definitively has XLH.** Therefore, there would be no need for an additional iFGF23 testing in most patients with XLH. Moreover, the Kyowa Kirin Hypophosphatemia Genetic Testing Panel includes 12 additional genetic tests for other diseases that mimic XLH, helping to provide a differential diagnosis and prevent inappropriate treatment.

Consistent with the clinical trials, the iFGF23 test can also be used to help confirm an XLH diagnosis. While not solely diagnostic, the confirmatory iFGF23 test is especially useful to substantiate an XLH diagnosis when genetic results are equivocal (~10%) or unavailable.

Logistically, access to confirmatory iFGF23 testing in Canada is extremely limited. The Kainos assay is not commercially available and only used for research purposes. Therefore, the only current iFGF23 test available is through Mayo Clinic. *Mayo Clinic has conducted equivalency studies that demonstrate good correlation between their assay and the Kainos assay. However, the results from the Mayo assay are slightly lower than the Kainos assay. A cutoff of 22 pg/ml from the Mayo assay would be the equivalent to the Kainos assay cutoff of 30 pg/ml used in the Kyowa Kirin clinical trials.

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	☐

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

Addressing the second point: Page 5, Table 1, Point #9 of the draft recommendation:

> *"Burosumab must only be prescribed by an endocrinologist or rheumatologist with experience in the diagnosis and management of XLH."*

This condition for reimbursement leaves out a very important category of potential prescribers who possess expertise in XLH and may be already treating adult patients with XLH. Consideration should be given to adding nephrologists, internists and other physicians who are presently treating adults with XLH and who possess an expertise in treating rare diseases and/or metabolic bone disorders. The specialty of clinicians who treat patients with XLH vary by institution. We believe that restricting the prescription of burosumab in adults with XLH to only endocrinologists or rheumatologist fails to capture the breadth of experienced physicians who are currently following patients with XLH in a real-world setting.

In the first final CADTH recommendation from May 2020 for the pediatric XLH population, CADTH included the following for the "*Prescribing Conditions*" in the Final Reimbursement Recommendation:

"Burosumab should only be prescribed by a physician working in a comprehensive team of health care providers who are experienced in the diagnosis and management of XLH."

It is unclear why a limitation has been placed on who can provide care for adult patients and this could impact transition of care.

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

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  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☐
	Yes	☒
Help was obtained via Kyowa Kirin regarding the types and clinical availability on the different iFGF23 assays across Canada.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Melissa Fiscaletti*
Position	*Pediatrician, Medical co-director of bone clinic CHU Sainte Justine, Assistant Prof Pediatrics, UofM*
Date	*26-06-2024*
☒	**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 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

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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

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0818
Brand name (generic)	burosumab
Indication(s)	X-linked hypophosphatemic rickets
Organization	Kyowa Kirin
Contact information[a]	Name: Dr. Christopher Kovacs [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.

There are two significant problems with the recommendation (Table 1, Reimbursement Conditions and Reasons, Item 2).

First, where it is stated that patients should have "and both of the following," i.e., a PHEX mutation AND a certain intact FGF23 level. That should read that patients have a PHEX mutation OR a certain intact FGF23 level to be consistent with the clinical trial inclusion criteria, and to reflect that up to 60% of patients with confirmed XLH can have a "normal range" or even low FGF23 level at any one time depending upon their treatment stage and their inherent sensitivity to FGF23. A "normal range" FGF23 value is inappropriately high in the setting of hypophosphatemia and therefore confirmatory of FGF23 excess. There is overlap of the XLH disease state with the ostensible "normal range" because of how the normal range was determined. See Hartley IR et al *JBMR Plus* 2022; 37(11): 2174-2175, which studied 434 subjects with and without known phosphate disorders. The cut-point with 100% sensitivity and specificity for FGF23 excess was 27 pg/mL, not the 30 pg/mL previously found by Endo and cited by CADTH using the Kainos assay. Moreover, if a patient has had multiple measurements of intact FGF23 done in the past (which is likely), the highest values should be quoted. What needs to be prevented is a situation where the most recent FGF23 value appears "normal" and then coverage is denied despite evidence of higher FGF23 levels in the past.

Second, the recommendation requires a measurement of FGF23 >30 on the Kainos assay. It does not specify if this is the ELISA vs. the chemiluminescent assay, which differ in performance characteristics. More importantly, within North America, the Immutopics/Quidel ELISA assay is commonly used now, as is the chemiluminescence assay from Eagle Biosciences and from the Mayo Clinic Laboratories. Decisions about which assays are used are made by hospital laboratories, not by physicians. Restricting the FGF23 value to be one done specifically on a Kainos assay will prohibit patients from accessing burosumab if their laboratory (or the reference laboratory they send out to) uses one of the assays commonly used in North America (as does my university hospital). Adding to the confusion, the assay developed by Kainos can be marketed under another name by distributors in North America, leading to the impression that the assay wasn't a Kainos assay when it was. I see from Table 1 that the sponsor might be required to arrange for the FGF23 assay to be done by Kainos, but that will still lead to the problem stated in my first point, above, that variability in FGF23 levels can lead to a patient with XLH variably having a "normal" level that is in fact inappropriate given the hypophosphatemia. If the patient finally has an FGF23 measurement using the Kainos

assay and it is not as high as prior values, the patient may be penalized as not having XLH when in fact the patient does have it.

Overall, I suggest:

1) Revert the criteria in #2 to change "and both" to "or one or both" so that it is "OR one or both of the following" with respect to a PHEX mutation and a particular FGF23 level.
2) The FGF23 level should be >27 pg/mL to reflect the updated analysis by Hartley et al.
3) A more inclusive policy that reflects the physiology of the situation would state "a high or inappropriately normal intact FGF23 level" rather than specifying >27 pg/mL as an absolute threshold that must be met
4) If a particular FGF23 value must be reached, state that it does not have to be a new value done at the time of seeking coverage for burosumab, but instead the highest value(s) previously achieved can be used
5) Delete reference to Kainos and state that it is an intact FGF23 value obtained using an FDA and/or Health Canada approved intact FGF23 assay

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? See my comments regarding point #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. See my comments regarding point #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. See my comments regarding point #1		
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	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
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3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
• N/A We did not provide any input previously		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Christopher Kovacs
Position	University Research Professor, Memorial University of Newfoundland
Date	24 June 2024
☒	**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
Kyowa Kirin	☒	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Burosumab
Indication(s)	Adult XLH
Organization	The Ottawa Bone Health Research Group at the CHEO Research Institute
Contact information[a]	Name: Leanne Ward

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.		

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. Section 2.2		
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. In Section 2.2, the reimbursement criteria state that an FGF23 level is required (in addition to a PHEX variant). However, a PHEX variant is sufficient to diagnose a patient with XLH. The requirement of a certain FGF23 level is not part of routine clinical care. Furthermore, FGF23 levels may not be high in XLH; this is referred to as "inappropriately normal FGF23 levels in the face of hypophosphatemia" (since FGF23 should normally be low when serum phosphate is reduced). Together, the PHEX variant is sufficient to diagnose a patient with XLH and to warrant treatment (without the FGF23 requirement), provided the other reimbursement criteria are met (including the low serum phosphate). In section 9.0, it is stated that burosumab can only be prescribed by an endocrinologist or rheumatologist; however, there are other individuals in Canada with expertise in the management of metabolic bone disorders, such as internal medicine physicians, geneticists, and nephrologists. Burosumab should therefore be prescribed by individuals with adequate training and expertise in		

metabolic bone disease. Evidence of proper training and therefore expertise can be demonstrated through licensure in a relevant specialty as listed above, or through courses or documented supervision by a known expert in the field.

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

Appendix 2. Conflict of Interest Declarations for Clinician 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.
- For conflict of interest declarations:
  - Please 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.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name Leanne Ward*
Position	*Please state currently held position Clinician Scientist, CHEO Research Institute*
Date	*Please add the date form was completed (27-06-2024)*
☒	**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**
Kyowa Kirin (for consultancy, with funds to the CHEO RI and CHEO Foundation)	☐	☐	☒	☐
Ultragenyx *(for operationalization of clinical trials + consultancy, with funds to the CHEO RI and CHEO Foundation)*	☐	☐	☐	☒
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	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0818
Name of the drug and Indication(s)	Burosumab (Crysvita) for the treatment of X-linked hypophosphataemia (XLH) in adult and pediatric patients 6 months of age and older
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. Clarification is needed in the reason for reimbursement condition 2. The condition requires patients to satisfy both 2.1 and 2.2, but the reason references the inclusion criteria for CL303, which only required patients to satisfy 2.1 or 2.2. As written, the reason doesn't appear to fully support the condition. Clarification is needed in the reason for reimbursement condition 4 to explain why patients with eGFR of 45 to <60 mL/min due to nephrocalcinosis do not appear to be eligible to receive

therapy, since reimbursement condition 6.2 lists nephrocalcinosis on conventional therapy as one of the reasons a patient would be able to access burosumab.
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. Guidance is needed for reimbursement condition 3 to indicate when the required biochemical tests should be measured in relation to intake of the conventional therapy (defined as active vitamin D and oral phosphate supplementation) required per reimbursement condition 6. In CL303, patients had not taken conventional therapy within 14 days prior to the second screening visit. If patients need to stop conventional therapy for the tests to be done, this needs to be outlined. Guidance is needed for reimbursement condition 9 to outline what the maximum reimbursed dose of burosumab should be.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0818
Brand name (generic)	CRYSVITA (burosumab)
Indication(s)	For the treatment of X-linked hypophosphataemia (XLH) in adult and pediatric patients 6 months of age and older
Organization	Kyowa Kirin Canada, Inc.
Contact information[a]	[redacted]

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

Kyowa Kirin Canada, Inc. (KKCA) agrees with the committee's recommendation to reimburse burosumab with conditions for the treatment of X-linked hypophosphataemia (XLH) in adult patients and appreciates the committee for recognizing the significant unmet needs in the management of XLH in adult patients, and the clinically meaningful impact of burosumab on serum phosphorus normalization, symptoms of pain and stiffness and fracture healing, thereby allowing patients to regain function and gain improvements in quality of life. However, KKCA notes that several of the reimbursement conditions place excessive restrictions to burosumab access, contradicts patient input that "*there is a need for treatment options that are accessible*" (page 8), and is not supported by clinical data.

The recommended Reimbursement Conditions (Table 1) notes that the diagnosis of XLH should be: "*supported by classic clinical features of adult XLH (such as short stature or bowed legs) **and both** of the following:*

2.1. a confirmed PHEX gene variant in either the patient or a directly related family member with appropriate X-linked inheritance

2.2. Serum intact FGF23 (iFGF23) level > 30 pg/mL by Kainos"

KKCA would like to highlight that this is contrary to the enrollment criteria of the pivotal Phase 3 RCT Study CL303, which was cited as the rationale for this reimbursement condition. As noted in Table 1 under the "Reason" column:

"*Study CL303 enrolled patients with a diagnosis of XLH supported by classic clinical features of adult XLH (such as short stature or bowed legs) **and at least one** of the following at Screening:*

1. *Documented PHEX mutation in the patient or a directly related family member with appropriate X-linked inheritance*
2. *Serum intact FGF23 (iFGF23) level > 30 pg/mL by Kainos assay"*

The enrollment criteria for Study CL303 had a minimum requirement for either documented *PHEX* mutation or an abnormal serum iFGF23 level, in addition to classical clinical disease features. Notably, the recommendation states that "*CDEC agreed with the clinical expert that the study inclusion criteria identify patients with symptomatic XLH and are applicable to patients in the expert's*

context" (page 9). Therefore, the reimbursement condition for both a confirmed *PHEX* gene variant and an abnormal serum iFGF23 level deviates from the inclusion criteria of Study CL303 and contradicts clinical expert input received by CDEC. To the knowledge of Kyowa Kirin (Global), the Kainos assay required for iFGF23 testing, as noted in Table 1, is not commercially available, as it is used only for clinical research purposes and would therefore create barriers to diagnosis and treatment for adult patients with a positive XLH diagnosis confirmed by a *PHEX gene* variant. Any testing for serum iFGF23 currently needs to be sent outside of Canada, using alternative assays (such as the Mayo Clinic iFGF23 assay), with different reference ranges that will likely lead to confusion in the interpretation of the assay results and possibly the inappropriate denial of reimbursement requests for adult patients with XLH. Moreover, measuring iFGF23 serum levels is not required for the diagnosis of XLH but should instead be used as a confirmatory test in cases where *PHEX* genetic testing results are equivocal. Upon a negative *PHEX* test, iFGF23 measurement would be conducted as a differential diagnostic tool to confirm negativity of *PHEX* variant, alongside other biochemical measurements and clinical evaluations. Of particular concern is excessive testing requirements that could disproportionately impact patients living in remote areas, leading to treatment access inequity. KKCA proposes that the reimbursement condition be revised to reflect the inclusion criteria of Study CL303 that required ***one of*** a documented *PHEX* gene variant ***or*** an abnormal serum iFGF23.

The Reimbursement Condition related to prescribing of burosumab in Table 1 ("*Burosumab must only be prescribed by an endocrinologist or rheumatologist with experience in the diagnosis and management of XLH*") may further present unnecessary barriers and delays to effective treatment for adult patients with XLH. The optimal care of symptomatic patients with XLH may require the involvement of several targeted specialties (i.e., endocrinologists, nephrologists, rheumatologists, geneticists, and potentially others) in the prescribing of burosumab. As such, the prescribing of burosumab should not be restricted to the two identified physician specialties as listed in Table 1. Instead, KKCA proposes that the prescribing condition for burosumab in adult patients with XLH mirror the condition outlined in the 2020 CADTH recommendation for burosumab in the treatment of pediatric patients with XLH: "*Burosumab should only be prescribed by a physician working in a comprehensive team of health care providers who are experienced in the diagnosis and management of XLH.*" [1]

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	☐

In general, the recommendation considers most of the feedback that KKCA provided to CADTH during the review process.

Clarity of the draft recommendation

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

KKCA believes that the reasons for the recommendation are clearly stated which are based on significant unmet needs in adult patients with XLH and the clinical evidence demonstrating the efficacy and safety of burosumab in the treatment of XLH.

The recommendation notes that "*XLH is associated with significant morbidity; is a rare disease; current therapy only targets downstream effects of the disease mechanism and is susceptible to reduced efficacy via a feedback loop; and the majority of patients continue to have symptoms according to the clinical expert*" (page 6).

Furthermore, based on the submitted clinical data, "*CDEC concluded that burosumab potentially met a number of patients' needs and provided enough evidence to suggest a meaningful impact to*

patients, noting potential improvements in domains such as pain interference and stiffness, along with improved fracture healing" (page 3).

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

The recommendation clearly describes the implementation issues noted by drug programs and provides sufficient response to addressing most of the concerns.

However, in response to the drug programs question around use of CL303 inclusion criteria as reimbursement criteria, CDEC recommends that "*Diagnosis of XLH be supported by classic clinical features of adult XLH (such as short stature or bowed legs)* ***and both*** *a confirmed PHEX gene variant in either the patient or a directly related family member with appropriate X-linked inheritance* ***and*** *Serum intact FGF23 (iFGF23) level > 30 pg/mL by Kainos assay, rather either a confirmed PHEX gene variant or Serum intact FGF23 (iFGF23) level > 30 pg/mL*" (page 10). CDEC does not provide a clear rationale for recommending reimbursement criteria which deviate from the trial inclusion criteria of Study CL303. As noted in the response above, this reimbursement condition places unnecessary restrictions which may prevent access to burosumab, is not supported by clinical trial data and does not reflect Canadian clinical practice in the management of patients with XLH.

To Kyowa Kirin (Global) knowledge, the Kainos assay noted in the recommended reimbursement condition for iFGF23 testing is not commercially available, itis used only for clinical research purposes, and would therefore create barriers to diagnosis and treatment for adult patients with a positive XLH diagnosis confirmed by a *PHEX gene* variant]. Any testing for serum iFGF23 currently needs to be sent outside of Canada, using alternative assays (such as the Mayo Clinic iFGF23 assay) with different reference ranges that will likely lead to confusion in the interpretation of the assay results and possibly the inappropriate denial of reimbursement requests for adult patients with XLH Moreover, measuring iFGF23 serum levels is not required for the diagnosis of XLH but should instead be used as a confirmatory test in cases where *PHEX* genetic testing results are equivocal. Upon a negative *PHEX* test, iFGF23 measurement would be conducted as a differential diagnostic tool to confirm negativity of *PHEX* variant, alongside other biochemical measurements and clinical evaluations. Of particular concern is excessive testing requirements that could disproportionately impact patients living in remote areas, leading to treatment access inequity. KKCA proposes that the reimbursement condition be revised to reflect the inclusion criteria of Study CL303 that required ***one of*** a documented *PHEX* gene variant ***or*** an abnormal serum iFGF23.

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

The reimbursement conditions are clearly outlined in Table 1 of the draft recommendation. A clear rationale for the conditions is provided for the majority of the reimbursement conditions with a couple of notable exceptions, as indicated above in our comments for Question 1.

The reasons provided in Table 1 do not adequately justify the reimbursement conditions which require that the diagnosis of XLH be supported by both a confirmed PHEX gene variant and a serum iFGF23 level and the prescribing condition that burosumab must only be prescribed by an endocrinologist or rheumatologist. The optimal care of symptomatic patients with XLH may require the involvement of several targeted specialties (i.e.., endocrinologists, nephrologists, rheumatologists, geneticists, and potentially others) in the prescribing of burosumab. Instead, KKCA proposes that the prescribing condition for burosumab in adult patients with XLH mirror the condition outlined in the 2020 CADTH recommendation for burosumab in the treatment of pediatric patients with XLH: "*Burosumab should only be prescribed by a physician working in a comprehensive team of health care providers who are experienced in the diagnosis and management of XLH.*"

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

References

1. CADTH. *CADTH Canadian Drug Expert Committee Recommendation: Burosumab (CRYSVITA)*. 2020. Accessed June 20, 2024. https://www.cadth.ca/sites/default/files/cdr/complete/SR0602%20Crysvita%20-%20CDEC%20Final%20Recommendation%20May%2029%2C%202020_For%20posting.pdf