CADTH

CADTH COMMON DRUG REVIEW

Patient Input

BUROSUMAB (Crysvita)
(Kyowa Kirin Limited)
Indication: X-linked hypophosphatemia (XLH)

CADTH received patient input from:

Canadian Organization for Rare Disorders with support of XLH Network

March 15, 2019

CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Crysvita (burosumab-twza)**
Name of the Patient Group	**Canadian Organization for Rare Disorders with support of XLH Network**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

Canadian Organization For Rare Disorders (CORD)

CORD is Canada's national network for organizations representing all those with rare disorders. CORD provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. CORD works with governments, researchers, clinicians and industry to promote research, diagnosis, treatment and services for all rare disorders in Canada.

https://www.raredisorders.ca/

The XLN Network is a worldwide patient support organization for people living and dealing with X-Linked Hypophosphatemia (XLH). The mission of the XLH Network is to promote XLH awareness and education for affected families, medical professionals, and the community at-large; to support physicians and other providers of medical care for better diagnosis and treatment; to create resources and a community for affected individuals and their families so they can understand and cope with the complications of the disease; and to foster the search for a cure.

https://www.xlhnetwork.org/

2. Information Gathering

Recruitment: There is no established XLH Network in Canada but there are patients and families who participate in the international XLH Network, a registered charity in the USA. By connecting with the XLH Network leaders, we were also able to identify patients and family members in Canada. Overall, participants were recruited through three sources: a small "snowballing technique" started with direct requests to Canadian patients and families who then recruited other families; posting by the XLN Network in their Facebook page; and direct outreach by clinicians treating XLH patients in Canada, including those who had taken part in clinical trials for burosumab-twza (Crysvita).

Responses: Information was collected primarily through the survey but also three individual interviews with patients and parents who had experience with Crysvita. Overall, there were 70 responses to the online survey, with 60 also providing individual testimonies. All those who provided individual interviews or testimonials also completed the online survey. All affected Canadian patients and families were asked to complete the survey, regardless of their experience with Crysvita; however the outreach to patients through the XLH Network Facebook specifically encouraged those with Crysvita experience to respond, although it was clear that all patients and families were eligible

Among the 70 respondents, two thirds (67%) identified as a person diagnosed with XLH and another 4% said they were not (yet) diagnosed with XLH but had symptoms consistent with XLH. About one-fourth (27%) of survey respondents identified as caregivers for someone with XLH (20% parents and 7% other family members, namely spouse or grandparent). One person was unsure as to her diagnosis and another indicated hers was a spontaneous case.

Diagnosis: Most of the respondents have been diagnosed for a long time. Almost all patients (87%) had been diagnosed under the age of 12 years old; about 4% said the patient was diagnosed between the ages of 12 and 18 while only 9% were over the age of 30 when they received a diagnosis.

In terms of time since diagnosis, the majority (80%) said the patient had been diagnosed for more than 30 years. About one-tenth (11%) said they had been diagnosed 18 to 30 years ago, while only 2% said they had received their diagnosis between three and 18 years ago, and another 4% had been diagnosed less than three years ago.

Demographics: While the expected gender ratio XLH is 2-to-1 females-to-males, the respondents to this survey were overwhelming female. Among the patients represented in the survey, 88% were identified as females and 12% as males. We have no explanation for these findings except that most respondents were themselves patients and it is possible that females are more likely to be engaged with the XLH Network Facebook than males. Because XLH is a genetic disorder, many of the respondents talked about generations of XLH in the family as well as impact on other relatives. However, it is important to note that many cases reported were spontaneous (mutations) with no history in the family.

Among those who specified a country of residence (66 respondents), 30% lived in Canada, 55% in the USA, and the remainder from various countries (Australia, New Zealand, UK, Norway, and Bermuda). Among Canadian respondents, about 38% (8) said they lived in Ontario, 29% (6) in Manitoba, 19% (4) in BC, and 5% (1) in each of Alberta, Nova Scotia, and Northwest Territories.

3. Disease Experience

To understand the impact of living with XLH, participants were presented with a number of open-ended questions, specifically, how XLH has affected you and your family; impact on person affected… the family and others; and impact socially, financially, and psychologically.

Responses were content analyzed by categorizing statements according to themes. There was a high degree of consensus on the key themes. Symptoms mentioned by almost everyone were: chronic debilitating pain, bone and joint deformities in legs and spine, severe dental problems, fractures and stiffness, short stature, hearing problems, and osteoarthritis (with aging).

This disease caused pain as a child through my whole life and pain as an adult. My pain is in all joints, muscles and teeth.

She suffers from pain and was addicted to pain pills following a surgery at age 6. Her dental issues are painful and a huge financial burden.

I developed my first stress fracture when I was 15 years old, my first cast at 16, right when I was learning to drive. I continued to develop more stress fractures; so that by the time I was 28/29 I had four, one in each femur and one in each tibia. The pain, it sucked. I could not walk long distances without having to rest; it felt like I had shards of glass in my legs.

Males tend to experience more severe symptoms than females. [My son] did have the benefit of rocaltrol and K-phos since time of diagnosis at age 3 months. His legs are much straighter than mine. He does suffer from spinal stenosis, and thoracic facet pain, as well as debilitating Ménèrs episodes for the last two years, and has tinnitus fairly severe, and some hearing loss.

For older adults, the physical symptoms (bone and joint damage) accumulate, as do the psychological impacts.

As an adult I am prone to calcium deposits in my joints, which can be painful, and limit functioning. I have undergone one arthroscopic surgery of one knee, and should have the other done. I need to have arthroscopic surgery of my shoulder. My XLH has also affected my hearing. I have single sided deafness, and have experienced Ménèrs disease, which can be a side effect for some.

Due to severe malformation of my back/ spine and knee, I live with constant pain and yes, shame. It has worsened considerably when entering my seventies.

XLH has significantly limit[ed] my mobility. I have to walk with additive devices at all times, have had several falls and broken bones along with severe pain. I need help daily from my family and need help with my personal hygiene care. XLH impacts myself and my family every minute of every day.

The treatments were often experienced as onerous as the primary symptoms: plates inserted in legs of growing children to straighten their legs, corrective surgery especially on legs and spine, medications (requiring frequent dosing but also with horrible taste), and calcium deposits as a result of medications. Parents and patients all spoke to the social, educational or work challenges, financial difficulties as well as psychological impact.

One major challenge for everyone is the time required to manage the disease. Parents spoke to the time required, not only for the diagnosis, testing, and treatment but also the time to get to specialty sites, up to three to four hours. This translates to time taken from work for the patients and family members, which also leads to a financial impact. XLH is also a costly disease since some of the medications are not covered by insurance (over the counter). Parents talked about the challenge of the “three-to-seven times-a-day” dosing, which also meant the child needed to be dosed while at school and also during the night.

Until the new medicine became available, she had to take phosphorous 5 times a day, along with the active form of Vit D... starting at age 2! Very difficult getting her to take the non-palatable mixture, and, having to remember to take each dose (planning, prepping, making sure you got home in time for the next dose if you hadn't planned ahead) was very taxing on us as parents. Financially, the over-the-counter treatment was expensive, as it wasn't covered by insurance.

There are no words for the pain of watching your beloved baby grow to a toddler with bowed legs and extremely painful bones, of forcing medications on a baby that when I tried drinking it, I couldn't. It was that strong. My beautiful loving granddaughter still grew up with twisted bones and under 4 feet 10 inches. She has had pins put in her knees to support her weight, spent months in Hospital with bone infections and has suffered greatly with pain.

Our 5yo daughter requires treatment 7 times a day, physio daily and regular hospital and dental appointments. She's in pain and tires easily. She cannot keep up with other children. She wants straight legs and requires major surgery next month on her legs

She was medicated 5x throughout the day and night. This was difficult as we had to wake her after midnight to medicate her and then again early in the morning. She required medication at school each day and the school was not consistent in administering it. We ended up removing her from the school to ensure she receives her medication.

As a person living with XLH, I have bowed legs, and short stature, stiffness in my legs particularly if I have been sitting for a long time. I had corrective surgery on both legs as a young teenager, after the doctors said that I had stopped growing. Since childhood, I have needed to take numerous medications throughout the day, to help improve my phosphorus levels, and maintain bone mineralization.

To gain a “quantitative” insight on the challenges of XLH, participants were also presented with a list of problems or difficulties associated with XLH, and respondents were asked to rate the degree to which they experienced difficulties or problems with each, on a five-point scale identified as “no problem, never”, “minor, infrequent”, “moderate, sometimes”, “serious, frequent”, and “incapacitating, regularly.” The symptoms rated as most difficult were “joint pain and stiffness” with more than half (53%) reporting the

impact was “serious” or one-third (33%) as “incapacitating.” Average rating of difficulty was 4.2 (out of 5). Almost equally problematic was “rickets or softening of the bones” with about half (50%) responding it was “serious” and another one-third (30%) reporting the impact was incapacitating, and an average rating of 4.0.

There were three types of problems that were regarded as almost equally challenging with 60% to 80% of respondents rating these “serious, frequent’ or “incapacitating, very often): “fatigue, muscle pain and weakness”, “tooth abscess and dental pain”, and “curved, bowed legs or knocked knees.” Average ratings were 3.8 to 3.9. Almost NO respondents said these were not problems for them personally.

Slightly less impactful were three other types of issues: “fractures and pseudo fractures”, “headaches” and “hearing loss”, with about 35% to 40% reporting these as “serious” or “incapacitating” and 35% to 45% indicating they experience these problems as minor or not at all. Least impactful were spinal stenosis (not a problem for about half and serious or worse for about one-fourth) as well as “irregularities in the shape of the head” which were minor or no problem for about three-fourths (75%) and serious or worse for one-tenth (11%).

Overall, most of the patients experienced multiple symptoms and many experienced them as serious or worse. As noted in their open-ended responses, the challenges of dealing with severe pain and other physical symptoms were compounded by the surgeries and medication regime and the additional challenge of the time and difficulties for accessing treatment, all of which have serious deleterious impact on quality of life for the patient and family, including the ability to engage in daily living activities and to sleep through the night, enjoy most forms of physical activity (due to pain and/or fatigue), the ability to attend school or work, to ability to participate in regular social and/or family activities, and the need to deal with considerable expenses, including medication.

My child was diagnosed at age 4 and started …(oral phosphate and calcitriol). She suffered severe bone pain and muscle weakness. Her legs were bowed and … she became knock kneed. She had surgery at age 9…. She is now a teen ager and … still has some twist to her thighs that cause her feet to turn in. She is very self conscious … has been teased by kids because she trips over her own feet. She was medicated 5x throughout the day and night. This was difficult as we had to wake her after midnight to medicate her and then again early in the morning. She required medication at school each day and the school was not consistent…. We ended up removing her from the school. The medication tasted awful, it was difficult to go to birthday parties and sleepovers ... We lived our lives around that medication schedule…. It was a huge challenge. I gave up my full time job and have worked part time since her diagnosis as it makes it easier to attend her appointments and then the surgery. I was able to be home with her when her legs hurt too much to sleep and then go to school. Her doctors are 1.5 hours from our home. So, we have suffered a loss of income…. Our private insurance does not cover the cost of phosphate. So we paid out of pocket for years.

4. Experiences With Currently Available Treatments

Specific treatments: benefits, side effects and management: Prior to Crysvita, there were no specific therapies for the treatment of XLH. Survey respondents were presented with a list of potential treatments (medications, dental procedures and surgery) and asked to indicate whether they used in the past, were using currently, or had used, with an option for “not sure.” All the medications listed were those used to manage symptoms, including pain and fatigue, and to augment phosphate and calcium to reduce the impact on bone strength and structure. Almost all of respondents reported having received, currently or in the past, phosphate supplements (92%) and Calcitrol calcium supplements (88%). Similarly, most had or were currently receiving Vitamin D supplement. Almost none had received growth hormone therapy (12%).

In terms of corrective therapy, almost all (98%) reported receiving dental procedures (often very serious and invasive including numerous root canals, dental replacements, and on-going corrective dental intervention. Most (60%) had received some corrective surgery on the legs, including some spinal surgery) while only 10% reporting any surgery to address skull deformities.

Effectiveness: Respondents were asked to rate the effectiveness of each therapy in managing XLH symptoms, on a five-point scaled anchored by “not at all” to “very well.” Frankly, it was hard to judge the

context used by respondents for making these ratings, since most (prior to Crysvita) spoke of disease progression and decreasing mobility and quality of life, despite the supplemental medications and surgical interventions.

In terms of interventions, respondents were most positive about the impact of dental procedures, with about one-third (33%) rating them as performing "well" or "very well" in addressing the presenting symptoms or problems. Among those who had received corrective surgery on their legs, only about one-quarter (27%) felt the intervention had worked "well" or "very well" to address the problem, and a similar percentage indicated "somewhat" effective impact. Among those who had received surgery on the skull to address deformities, they were equally split in terms of effectiveness, with half reporting the procedure had worked "well or very well" while about half said the impact was "moderate", "poor" or "not at all."

Among those taking phosphate and calcium medications, only about 10% felt they worked "well" or "very well" while the majority felt they were somewhat (30% to 40%) effective and others feeling they had poor impact (about 40%). The feedback on Vitamin D was about the same with a slightly larger percentage rated the benefits as "not at all."

Overall, existing therapies (prior to Crysvita) had only, at best, moderate benefit on addressing symptoms or reducing disease progression with many feeling the impact was limited or very limited. This was expressed by patients (and caregivers) for patients at all ages, though the impact of the disease was progressive and older adults were considerably less mobile, less engaged, and more depressed.

The phosphate and Calcitrol helped to keep up her levels of phosphate. It did not take away the bone pain and muscle weakness. It has caused elevated PTH and calcifications in the kidneys. It did not help her growth rate and she still required surgery to correct her knock-knees.

They are not effective at all AND they have significant side-effects (kidney calcification, hyperparathyroidism and the less catastrophic but still troublesome gastrointestinal distress).

5. Improved Outcomes

More than two-thirds of respondents said they knew Crysvita well or very well with less than 5% reporting they had not heard of the new therapy. Most expressed expectations that drug will reduce or eliminate the symptoms, including pain, bowed legs, fractures, and fatigue, and most importantly, stop disease progression because it addresses the underlying cause.

All people with XLH should have access to Crysvita. The studies in the US have shown that children on Crysvita do not suffer from as much bone pain and muscle weakness and have increased energy. They also have an increased growth rate compared to kids on the standard treatment.

Adult studies have also shown a decrease in bone pain and muscle weakness and increased energy.

Crysvita is the first medication for this condition to actually address the problem at the cellular level. I expect the medication should eliviate [sic] symptoms depending on how early it is started. Children who begin the medication could retain the phosphorus their bones crucially need and face the possibility of leading a very "normal" life. I feel all XLH patients should have access to Crysvita since the disease is progressive. The earlier the medication is started, the earlier deterioration of the bones can be halted.

As an adult, Crysvita may provide [redacted] *with relief of the pain, the energy to be more active which should then also assist with her ability to work on her range of motion. She is a young lady who has years ahead of her. Our hope is that they are not years of more pain*

I believe that if our daughter was on Crysvita, she would have avoided surgery because other children her age who are on it now have straight legs. I believe she would be in much less pain too.

I know adults who have not had Crysvita and most of them are in severe pain. Bone pain, muscle pain, limited mobility. It's terrible. It breaks my heart to think this medication is in existence, but not available to all XLH patients.

I think all XLH patients should have access to Crysvita, both children and adults. Many of us are told, when we turn 18 or 21, that our XLH will not be a problem and that we don't have to treat it anymore. This hurts us. Adults need treatment just as much as children do. Treatment helps us retain our quality of life.

6. Experience With Drug Under Review

Overall, Canadian patients were as aware of Crysvita as their American and other international counterparts, with only 10% have little or no awareness. However, access to the therapy is considerably different. For the respondents as a whole, about one-third (23) had received or were currently receiving Crysvita; among these, 20 were from the USA or other countries and only three from Canada. The Canadian patients had accessed Crysvita through clinical trials. The American patients had access through clinical trials, compassionate access, and funding through various private and public insurance programs.

Comparison to others: benefits and disadvantages and impact on patients and family:

Patients were asked to discuss the most important benefits and how the therapy has affected their lives and their family. Patients were overwhelmingly positive about the impact on pain, fractures, dental problems, and mobility. Even adults with existing damage reported {dramatic} improvements in capacity and patients reported fewer or no new damage.

When I started Crysvita I had a fracture in my right hip and a stress fracture in my left hip and two in my right foot. Within 6 months, all of those were healed. Yes, all of them. The pain from my hips dictated how I slept, how far I could walk, even how I stood up and my gait.

Now, I walk so fast my friends have to keep up with me. I stand up with no hesitation, I explored San Francisco without having to rest. I am just like anyone else.

I was sceptical at first but since my body has adapted to it, I have seen some surprising (to me) changes. I haven't been to the dentist since I began Crysvita (previously I was at the dentist every other month or so, needing a new root canal or dealing with tooth pain). My body still hurts, due to arthritis, but not nearly as much.... I've found that I'm sleeping better and have more energy and clarity of mind. I'm not sure if those effects are from Crysvita or just a decreased pain, but my life is better.

My calcifications have stopped worsening, the spinal spasms have all but gone away (once or twice a year instead of almost daily), and I have more energy and virtually no bone pain.

My body has already been ravaged with the effects of XLH. While on Crysvita my pain levels were less, my fatigue was greatly reduced, and life in general was a bit improved which had a very positive impact on my emotional health as well. Since being off Crysvita for 5 months now, I have increased bone pain particularly in the long bones of my arms and legs. I'm fatigued and fall asleep most evenings when watching programs on television.

Most of the patients receiving Crysvita reported experiencing no side effects and none reported having side effects that were serious or unresolvable. A few reported injection site rashes or irritations when first using; a couple of others experienced occasional nausea. Three patients reported restless leg syndrome (which was bothersome but *"a fine trade-off from pain relief."*

7. Anything Else?

About 97% of respondents said they felt it was very important for all appropriate XLH patients to have access to Crysvita; the remainder said it was "important." Several characterized the therapy as "life-changing", allow individuals to "live a normal life", freedom from seeing their children in pain and taking medication 24/7 while watching life on the sidelines. About 90% said they would be willing to enrol in a follow-up program if on therapy.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No, the survey and analysis were conducted by the Canadian Organization for Rare Disorders

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No, we had no help outside of our group to collect or analyze the data.

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
NONE				

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.

Name: Durhane Wong-Rieger
Position: President & CEO
Patient Group: Canadian Organization for Rare Disorders
Date: 18 February 2019