

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: belzutifan (Welireg)

Indication: for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated non-metastatic renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, and non-metastatic pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

Name of Patient Group: The Canadian VHL Alliance with: The Canadian Organization for Rare Disorders, Kidney Cancer Canada, Pancreatic Cancer Canada, and the Canadian Neuroendocrine Tumour Society

Author of Submission: Stephen Parrott Chair, Canadian VHL Alliance with assistance by Durhane Wong-Rieger, President CEO of The Canadian Organization for Rare Disorders

1. About Your Patient Group

Describe the purpose of your organization. Include a link to your website.

The Canadian VHL Alliance (CVHLA) <https://www.cvhla.ca> raises money for research, provides education and support to Canadian VHL patients and their families, and advocates for improved treatment for patients with VHL disease.

The Canadian Organization for Rare Disorders (CORD) <https://www.raredisorders.ca/> 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.

Kidney Cancer Canada www.kidneycancer canada.ca is a national community of patients, caregivers and health professionals who work to provide every Canadian touched by kidney cancer with support, education and advocacy for their care pathways and treatment options.

Pancreatic Cancer Canada <https://pancreaticcancer canada.ca/> raises funds to ensure ground-breaking research, provides patient support services, education and raises awareness, with the goal to improve the rate of pancreatic cancer survival.

The Canadian Neuroendocrine Tumour Society (CNETS) <https://www.cnets.ca> was formed in 2007 to assist the Canadian neuroendocrine cancer community. CNETS supports patients through education, peer-support programs both in person and virtually, and helps patients navigate the Canadian healthcare system. CNETS increases awareness about neuroendocrine cancers among the general population and the medical field, fundraise for research, manage their own annual research grant competition and advocate on behalf of patients for access to cutting edge treatments and diagnostics Canada-wide.

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

In December 2022 CVHLA and Kidney Cancer Canada, conducted an online survey of patients and caregivers to assess the challenges VHL patients and caregivers face because of the disease. 123 patients and caregivers participated in the survey as follows:

Patients living with VHL: n=72 (59%)

Someone providing care to a person with VHL disease (either currently or previously): n=51 (41%)

Through this survey CVHLA identified 19 patients who had experience with belzutifan for the treatment of VHL disease.

Additionally, semi-structured telephone interviews were conducted with three patients and caregivers who have experience with the treatment under review.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Summary

Overall, patients described living with VHL as an on-going series of physical and psychological struggles. Because VHL tumours can grow in different parts of the body (spine, organs, and brain), the symptoms are varied. Numerous participants reported not getting a diagnosis until the tumours had advanced causing serious problems affecting vision, hearing, and walking. They experience considerable discomfort, pain and interference with carrying out everyday activities.

Psychologically, knowing you or a family member has VHL is a source of constant worry and stress, in part, because it is a "hidden condition." Some VHL patients reported their initial symptoms were dismissed or misdiagnosed by their local physicians; others said they were the ones who educated their healthcare providers in order to get access to appropriate care and services. Participants also talked about the huge burden of adhering to tumour screening guidelines, scheduling numerous different kinds of tests, sometimes traveling to major centres for tumour screenings, and paying for all of the expenses not covered by public

healthcare or even private insurance. In fact, they often had to “fight” with the insurance companies to cover essential medicines.

Moreover, because tumours have to be monitored regularly, many VHL patients reported worrying about the potential adverse effects of frequent screenings (contrast, electromagnet images) as well as the stress caused by the “uncertainty” of tumour activity between scans. Overall, participants expressed the view that receiving a scan result rarely provides a feeling of “relief”; there is no such thing as a “good news” scan result since the best-case scenario is a report of “no change” in the tumour (it doesn’t go away on its own and can continue to grow).

What we heard was that unlike most single-site cancers where a “five-year cancer free” test result means no further screenings or worry, VHL is, at best, a lifetime of uncertainty.

Patients experience VHL as excruciatingly painful and debilitating, with cysts and tumours that can attack throughout the body, including the spine, brain, kidney, pancreas kidney, eyes/retina, epididymis, adrenal glands, endolymphatic sac, spine, brain/brainstem/cerebellum, neck, breast, inner ear, choroid arteries, jugular vein, lungs, duodenum, and groin. They also experience serious disruption to daily life and quality of life, including diminished ability to care for themselves, to engage in family and social activities, to plan for a family, and to participate in work. The last also affects their finances, feelings of self-worth, and engagement in meaningful activities. Given that the only treatment is surgery, it is not surprising that the overwhelming majority of patients have endured multiple surgeries on multiple sites, some with tremendous life-threatening risks. And, of course, it is not feasible to surgically remove tumours at some sites, such as the spine and the brain.

Detail

In our survey, overall, about 45% of participants reported a negative impact “4” or “5” on each of these activities, your ability to:

- Work,
- Travel,
- Exercise,
- Conduct household chores,
- To spend time with family and friends and
- To fulfill family obligations.

We asked: ***Please let us know how surgeries have impacted your ability to work or your quality of life, including spending time with loved ones.*** 92 patients and caregivers provided commentary, some taking belzutifan.

- *One mother’s experience*
 - *I have had to watch one daughter go through losing their adrenal glands at age 18 & go on replacement steroids & enzymes daily & Lanreotide injections monthly & almost died due to H1B flu & strep & sepsis & lost lung, kidney, heart function & had to be put into a coma to*

survive due to lowered immune system. She had to decide to not have children due to VHL & damage done during surgeries & scar tissue from her pancreas surgeries betting attached to her reproductive organs & needing a hysterectomy. She is now in her late 40s & because of the replacement steroids she has a shrinking brain of a 70-year-old & bone loss due to osteoporosis brought on by the steroids. She also has eye & brain tumors that are being watched. She is also getting many other disabilities due to being immuno-compromised.

- *My other daughter has had one adrenal gland removed & part of the other & her spleen removed, etc. so she is immuno-compromised. She also has brain & eye tumors that are being watched. Now she has managed to have 2 children & one of the 2 has VHL & has had abdominal VHL surgery at age 12. I know how that horrible feels due to my children being 11 & 18 during their 1st surgeries & me being 6. Most of our tumors are found with MRIs but the kidney tumors need CT scans to define them before surgery & now every 3 months due to being on belzutifan trial. So, even more radiation, which has been shown to cause kidney cancer, etc.*
- *Please approve belzutifan, so we can stop having so many invasive surgeries & procedures like RFA (radio frequency ablation) & radiation causing scans in our future. We are running out of organs to remove or partially remove & getting too much radiation.*
- *Surgeries are very tough on the body and often very tough side affects.*
- *I was born with VHL, passed on from my father who passed away when I was 2 due to VHL. I hope to find a cure for me and my child that inherited it.*
- *My daughters & I all are immunocompromised due to our spleens being removed, etc. & needing to get the Splenectomy vaccines on top of flu, pneumonia, covid, Shingrix, Prevnar 13, etc.*
- *Belzutifan is our kind of our last-ditch effort to slow down the bus.*

For more patient experiences please see Appendix A.

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Summary

Belzutifan is the only approved treatment for patients with VHL disease and associated RCC, central nervous system (CNS) hemangioblastoma, or pNET that does not require immediate surgery.

When asked about the number of surgeries experienced, prior to the introduction of belzutifan, numerous patients reported that they had had so many surgeries they were only able to say, “*don’t know*”, “*multiple*”, “*too many to remember*”, or “*lost count*”. Based on the 98 individuals who provided quantifiable responses, a total of 520 surgeries had been experienced, with 18 individuals (18.4%) reporting 10 or more surgeries. The average number of surgeries was 5.3. Sadly, many patients qualified their count as the number “*so far*”, signaling more surgeries could be expected.

Among the most terrifying and high-risk surgeries that participants talked about are laser eye surgeries. Worse, many patients reported that their eye tumours could recur, necessitating repeated surgeries, with one patient reporting 24 laser eye surgeries to date.

Detail

Surgery remains the primary treatment for symptomatic lesions in VHL-disease.

Of the 112 individuals who answered the question, **85% (n=95) reported having had surgery to remove VHL cysts and tumors**, with 6% (n=7) reported having had no surgery, and 9% (n=10) reported that they have “NOT YET” had surgery.

87 individuals reported multiple tumor sites ranging from 2 to 8 sites. Based on the data collected, the average patient had tumors in 2.8 “sites”. However, many patients reported more than one tumor in one location/site. The sites reported included: *kidney, pancreas, eyes/retina, epididymis, adrenal glands, endolymphatic sac, spine, brain/brainstem/cerebellum, neck, breast, inner ear, choroid arteries, jugular vein, lungs, duodenum, and groin*. Patients reported not only having tumors resected, but in various cases having a whole kidney or lung removed.

We asked: ***How many surgeries have you (or the patient you care for) had with respect to the removal of VHL cysts and tumors?***

98 individuals provide data that we were able to use. Unfortunately, numerous patients had so many surgeries that they reported comments like: “*don’t know*”, “*multiple*”, “*too many to remember*”, or “*lost count*”.

Of the 98 individuals that provided usable numeric responses, there were a total of 520 surgeries reported, with 18 individuals (18.4%) reporting 10 or more surgeries.

The average number of surgeries reported = 5.3.

Some patients emphasized that the reported number was “*so far*” indicating that more surgeries were anticipated.

Many patients reported multiple laser eye surgeries in addition to surgeries in other locations on their body, including one patient who had 24 laser eye surgeries.

Many respondents spoke of the impact of surgeries on **“your ability to work or your quality of life, including spending time with loved ones.”**

Specifically, they said:

- *Surgeries and threat of surgeries has made everyday a struggle. Some physically as the surgeries have limited my ability to do the things, I once enjoyed like running and sports. Some mentally as the fear of surgery or possible surgery has affected every life decision I have ever made.*
- *Confined to wheelchair following brain surgery. Needs fulltime personal care. Low quality of life.*
- *The surgeries have impacted my work, quality of life and including spending time with loved ones quite a bit. I have struggled with pain on a daily basis, and it is hard to be active.*
- *Because the surgery location is a cerebellar tumour, there were many concerns about the side effects and whether I would be able to live again after the surgery.... I had to quit the company repeatedly due to symptoms and treatment. This results in hardship financially and mentally.*
- *I have had spinal cord surgery three times, all in the lumbar spine. With each surgery the scar tissue becomes more extensive.... causes pain and issues with sensation and strength. The doctors say the tumours are like salt and pepper all over the cord, from top to bottom. I'm terrified they will grow and require more surgery. I can't keep doing this ...*
- *It has forced me to take a lot of time off work over the years to have surgery and recover, which in turn has deterred me from going further in school or taken a more serious role at my current jobs.*

Caregivers reported:

- *Surgery on the brain stem tumours.... It took away their ability to swallow, walk, breathe without oxygen, speak clearly.*
- *The surgeries always impact the time we get to spend together because he's away for surgery and then trying to recover at home. It has impacted the time we spend with him because he is so sick. He is away so much for medical reasons he's missing out on so much family time. And as for work, he is not at all able to work. He has been sitting at home for the last year too sick for work.*
- *The results of surgery impacted the patient and made him bedridden, and took away his ability to swallow, walk. Needed to used oxygen. Inability to speak clearly. Fighting pneumonia frequently. Needed all around care.*

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Summary

Patients with VHL disease overwhelmingly expressed the need for a treatment that can improve their physical condition by decreasing the size of (or stabilizing) tumours, reducing pain, improving breathing, offering long(er)-term stability or reduction of disease., and, most importantly, offering the opportunity to avoid surgery. Overall, patients indicated they were willing to tolerate moderate to severe side effects of a treatment that would allow avoidance of surgery to remove VHL related cysts and tumours.

Detail

Participants were asked to rate the importance of different types of outcomes in relation to a new therapy, from "not important" to "extremely important."

<i>Improvement to your physical condition such as decreasing the size of (or stabilizing) the tumour(s), reducing pain, improving your breathing N=89</i>						
1 (Not important)	2	3	4	5 (Extremely important)	N/A	Weighted Average (WA)
0pts (0%)	0pts (0%)	4pts (4.5%)	9pts (10.11%)	73pts (82%)	3pts (3.37%)	4.80

<i>Overall Improvement to your quality of life. N=89</i>						
1 (Not important)	2	3	4	5 (Extremely important)	N/A	Weighted Average (WA)
1pt (1.12%)	3pts (3.37%)	6pts (6.74%)	7pts (7.87%)	69pts (77.53%)	3pts (3.37%)	4.63

<i>Chance for long-term stability or reduction of disease. N=112</i>						
1 (Not important)	2	3	4	5 (Extremely important)	N/A	Weighted Average (WA)
0pts (0%)	0pts (0%)	1pt (1.12%)	10pts (11.24%)	76pts (85.39%)	2pts (2.25%)	4.86

<i>Opportunity to avoid surgery(s) for the removal of VHL related cysts/tumours N=88</i>						
1 (Not important)	2	3	4	5 (Extremely important)	N/A	Weighted Average (WA)
0pts (0%)	0pts (0%)	2pts (2.27%)	5pts (5.68%)	79pts (89.77%)	2pts (2.27%)	4.9

Moreover, respondents were also asked to rate the “severity of side effects” they would be willing to tolerate in order receive a surgery that would provide the “opportunity to avoid surgery.”

<i>Rate the severity of side effects that would provide the opportunity to avoid surgery N=88</i>						
1 (No side effects)	2	3	4	5 (Significant side effects)	N/A	Weighted Average (WA)
2pts (2.22%)	14pts (15.56%)	33pts (36.67%)	23pts (25.56%)	14pts (15.56%)	4pts (4.44%)	3.38

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

Summary

Given the known risks of surgery and the traumatic psychological and physical impact of tumour recurrence, the patient groups represented in this submission are unanimous in their recommendation that all patients with VHL should be given the opportunity to access belzutifan based on individual informed decision between the treating physician and the patient/family. Given the lack of clear biological and other criteria for belzutifan, we endorse individually approved access based on the clinician-patient assessment of the balance of risks and benefits of belzutifan versus other options (no treatment, surgery, and watchful waiting).

Obviously, patients with tumours in locations where surgery is not feasible or highly risky (spine, brain, eyes, nerves), patients who have had multiple surgeries, and surgeries with other underlying conditions or frailties, the drug should not be limited to these patients. Rather, the decision should take into consideration the clinical status of the patient, the location, severity and prognosis of the tumours, history of surgery and outcomes, psychological and mental health status of the patient, and other relevant factors.

The patient groups represented in this submission recognize that the evidence to date does not indicate that belzutifan can shrink or eliminate all tumours; nor does it prevent all tumours from recurring for all patients living with VHL. However, we also recognize that belzutifan does work to shrink tumours to the point of being no longer problematic and many patients have not had the tumours recur post-treatment. To gain more knowledge, we recommend that all patients receiving belzutifan should be enrolled in a patient monitoring program to collect on-going real-world data on beneficial and adverse outcomes, which will be analyzed to further develop the treatment guidelines and protocol. This “managed access” approach has a high probability of success if monitored by designated specialists with appropriate clinical support. It is not desirable to have patients wait for more clinical trials to be conducted or for more evidence to be collected through other “controlled” settings.

Patients living with VHL cannot afford to wait for access until there is greater “certainty” in terms of outcomes based on additional or expanded clinical trials. Patients living with VHL need to have the opportunity to benefit from extended periods of tumour-free “remission.”

Detail

In Appendix A we supply patient stories from interviews conducted in January 2023. These stories detail a few individual cases to illustrate how the disease and the resulting surgeries can affect all aspects of the whole family.

From the discovery of the disease, across the whole family, to losing loved ones, at a very young age, VHL is a devastating disease. Those that survive the death of a family member, must themselves endure surgeries that leave them in constant pain and often render them bed-ridden. The surgeries can introduce fear of anesthetic dementia, continuous pain and digestive complications.

The psychological impact from the surgeries, their resulting effects on physical and emotion resilience caused mental breakdowns. Living with these ailments can make working impossible, changing contributing citizens and families into those reliant on the provincial and federal subsistence programs, for the rest of their lives.

In one case, it was noted that 30 members of one extended family have VHL. Stories of nephews becoming paralyzed following brain surgery spread quickly. It is very tough psychologically to hear about that and know that you could be next. Now family members can talk about the 6-8 members of his family that previously would be going “under the knife” for tumours that threaten some significant aspect of their physiology, to those people starting the new drug belzutifan. We talked to a family where this good news and that some are already reporting very positive results can be mentioned as hopeful news.

Overall, 19 of the survey participants reported having had experience with belzutifan to treat VHL disease.

When asked to rate their *personal experience with belzutifan, the following ratings were received*".

How would you rate belzutifan's effectiveness in controlling your VHL disease? N=18						
1 (Not effective)	2	3	4	5 (Extremely effective)	N/A	Weighted Average (WA)
0pts (0%)	0pts (0%)	7pts (38.9%)	4pts (22.22%)	2pts (15.56%)	5pts (27.78%)	3.62

How would you rate belzutifan's side effects? N=18						
1 (Completely intolerable)	2	3	4	5 (Very tolerable)	N/A	Weighted Average (WA)
0pts (0%)	0pts (0%)	6pts (33.33%)	5pts (27.78%)	5pts (27.78%)	2pts (11.11%)	3.94

When asked about the *experience [of] side effects that were particularly difficult to tolerate*, the following responses were received.

- Seizures
- Low hemoglobin levels
- Anemia- very tired
- Nothing has been intolerable so far
- Headaches some dizziness and heart thumping
- Fatigue, but F has no adrenals

Participants were asked to rate on a five-point scale quality of life while taking belzutifan, from "low/seriously impacted" to "high/normal living."

How would you rate your quality of life while taking belzutifan? N=18						
1 (low/seriously impacted)	2	3	4	5 (high/normal living)	N/A	Weighted Average (WA)
0pts (0%)	0pts (0%)	5pts (27.78%)	9pts (50%)	1pts (5.56%%)	3pts (16.67%)	3.73

Participants were also asked to rate on a five-point scale the “tolerability” of eight specific side effects associated with belzutifan. The responses are as follows.

	1 - COMPLETELY INTOLERABLE	2	3	4	5 - VERY TOLERABLE	N/A	TOTAL	WEIGHTED AVERAGE
▼ Fatigue/lack of energy	0.00% 0	11.11% 2	16.67% 3	44.44% 8	16.67% 3	11.11% 2	18	3.75
▼ Nausea	0.00% 0	11.76% 2	5.88% 1	11.76% 2	35.29% 6	35.29% 6	17	4.09
▼ Anemia (low hemoglobin)	0.00% 0	17.65% 3	29.41% 5	17.65% 3	17.65% 3	17.65% 3	17	3.43
▼ Dizziness	0.00% 0	17.65% 3	17.65% 3	23.53% 4	11.76% 2	29.41% 5	17	3.42
▼ Headache	5.88% 1	5.88% 1	23.53% 4	5.88% 1	35.29% 6	23.53% 4	17	3.77
▼ Dyspnea (shortness of breath)	5.88% 1	5.88% 1	11.76% 2	23.53% 4	17.65% 3	35.29% 6	17	3.64
▼ Myalgia (muscle aches and pain)	5.88% 1	11.76% 2	29.41% 5	0.00% 0	35.29% 6	17.65% 3	17	3.57
▼ alanine aminotransferase increased (liver damage)	5.88% 1	0.00% 0	5.88% 1	5.88% 1	41.18% 7	41.18% 7	17	4.30

Finally, they were asked to provide open-ended comments about their experience. These are some of the comments received.

- *Very hopeful this drug will help all VHL patients.*
- *Hoping for great results for VHL patients.*
- *We have never had a normal scan until now.*
- *This medication is life-saving in more ways than one, access is vital, and should be granted to those with vascular tumours beyond just RCCs, as it has been proven to be incredibly effective at controlling and reducing the size of CNS tumours of the brain, spine and eyes, and endocrine tumours like pheochromocytomas, and pNETs as well.*

In response to the request for changes in long-term health and well-being due to belzutifan, experienced and expected, the following comments were received.

- *I am hoping for less surgeries and a longer life then my predecessors.*
- *We hope that it helps to give him more quality of life with less surgeries and hopefully less tumours*
- *Peace.*
- *If it can prevent more surgeries, this is a major improvement to well being as neurosurgeon has said no more surgeries*
- *as possible. Progression of tumours will result in full loss of bodily functions.*
- *Slow or stop the growth of VHL Kidney tumors specifically & hopefully the neuro-endocrine tumors associated with VH in my pancreas, adrenal gland & brain & paragangliomas.*
- *Life saving.*

We further asked: ***Can you tell us about your story and why access to belzutifan and future therapies are so important to you?***

- *My dad has had VHL for all of his life...he has had about 15 different surgeries either on his kidney, his brain or his spine. He has been sick for most of his life because of this. We pray that the belzutifan will help him to have more healthy days than not. It is so important to us for him to continue to get those belzutifan. His tumours have been growing so much before this, that they have turned to cancer, and given him more sickness, we hope that this will work for him.*
- *To keep my health the way it is currently and for my children and family members in the future. We have lost so many family members to VHL it's hard to keep going in life when you see you're own people falling over one by one with the same disease I am fighting*
- *I have seen many loved ones suffer from the symptoms that the tumours make and how it effects their quality of life and would love for you to help them as well as future generations fight this decease. There are too many children suffering from it as well and I hope you can find answers for them, thank you!*
- *VHL patients deserve the right to live their lives as far and as healthily as they can, and if there are treatments available that can prolong and improve their lives and reduce their pain and tumours, they should have a right to access those treatments. To deny them is inhumane and cruel. Access should be easily managed through an oncology team and factors like a patient's location, gender, race, social status, insurance, or income should have no impact on their ability to access lifesaving treatments like belzutifan.*

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

Summary

The use of belzutifan does not require companion testing.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

Summary

Many belzutifan patients noted significant improvements with eye tumours. We realize this is not an indication within this submission, but it cannot be understated how large a side benefit this is for patients.

We believe this multi-site, in many cases proactive therapy, which addresses the root cause of the disease, is transformative, and has the potential to dramatically alleviate the burden of surgery, improve patients quality of life, and significantly reduce the massive health care costs associated with surgeries and hospitalizations."

The physical and emotional pain caused by the disease, then surgeries, then the aftermath of the surgeries is tremendous. Losing Canadians productivity and enjoyment of life to this disease can stop now.

We hope that you can find a way to make this a reality.

In recognition that VHL is a rare genetic disease with significant unmet need, we urge CADTH to apply the recommendations framework that includes “Considerations for Significant Unmet Need” as described in the Procedures for CADTH Reimbursement Reviews (March 2022), section 9.3.1.

We also request that CADTH report (in the draft recommendation) how the considerations for significant unmet need were applied in the review process.

Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, 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, we did not get any outside help to prepare this submission.

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 did not get any outside help to collect or analyze the data.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range with an X. Add additional rows if necessary.

Organization	Company	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
CVHLA - Sponsorship of 2022 International VHL Medical Symposium	Merck			X	
CORD	Merck			X	
KCC	Merck				X
PCC	N/A				
CNET	N/A				

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: Stephen Parrott

Position: Chair, CVHLA

Patient Group: CVHLA, CORD, KCC, PCC, CNETS

Date: February 21, 2023

Appendix A

Patient Stories:

KS (Patient, interview date Jan 30, 2023.)

KS is a 70-year-old woman living in Surrey BC. She was 6 years old when it was apparent that she had VHL as tumors were discovered on her adrenal gland. In her family, her father had VHL, with she and her two brothers also inheriting the syndrome. One brother died at the age of 18 as a result of VHL related surgery. Her two daughters and one grandchild also have VHL.

KS reports having used drug therapy and having undergone seven surgeries for the removal of cysts and tumors throughout her body, including in the: kidney, pancreas, adrenal glands, and brain, and an additional 10+ eye surgeries, having eventually lost one eye. One surgery resulted in damaged to her spine resulting in enduring pain and the need for intensive physiotherapy.

More recently, growing tumors were causing severe sciatica resulting in her being bed-ridden for 6 or 7 years. Finally, she had yet more abdominal surgery where they removed the body and tail of her pancreas, spleen, gall bladder and a paraganglioma from between her vena cava and aorta and removed a tumor from her left kidney.

Unfortunately, there is still tumor growth and now KS has pancreas NETs and (clear cell) renal cell carcinoma.

KS reports that VHL has had significant impact on her ability to work, travel, exercise, conduct household chores and spend time with family and friends.

- Each time I go under anesthesia it is one more step towards anesthetic dementia. Each CT scan I receive more radiation and more chance of my kidney tumors going cancerous. I had to retire early due to VHL adrenal and brain tumors causing me to have a mental breakdown at work due to stress and vertigo. I had to go for lots of therapy and I still see a psychiatrist monthly and take psychiatric medications to function well in society and at home.

KS also reports that VHL has had tremendous impact on her financial well-being. When she was younger, as a single mother, she had to pay for childcare and/or seek accommodations for her children during her many surgeries and recovery times. She also reports having had to use holiday and sick days and having to go on Employment Insurance or disability insurance or welfare to accommodate scheduled surgeries and recovery. Eventually she went on CPP Disability which was only good until she reached the age of 65. At that age she was switched to CPP, and her income has dropped drastically even though her actual level of disability has increased. She also reports having had to pay out-of-pocket for three new replacement eye orthotics (made by an Ocularist) as BC medical insurance does not reimburse for eye orthotics.

Experience with belzutifan

KS strongly advocated for access to belzutifan and is now taking 120 mg a day. belzutifan has had tremendous impact on her two brain tumors, with one disappearing completely, and the other having shrunk by half. She also reports that her vertigo has disappeared since commencing treatment with belzutifan. She

has much hope that belzutifan will shrink (or halt the growth of) the remaining tumors in her kidney, pancreas, adrenal glands and brain. She also is holding out hope that this drug will be made available to her children and grandchild and future generations. KS says:

- ***We VHL Warriors need something other than surgeries and invasive procedures throughout our lives to slow or stop the growth of these tumors.***

JT (Caregiver, interview date Jan 30, 2023.)

Patient is her husband: FT.

JT is the caregiver to her husband “FT”. They are both in their 50s.

FT’s mother discovered she had VHL in 1970 after a series of surgeries and ultimately losing vision in her right eye. She had already had three children at that point (including FT). As a result, it was assumed that the three children had VHL, which was later confirmed through genetic testing. One of FT’s brothers developed a brain tumor and subsequently passed away. FT’s sister developed a pancreatic tumor. FT and JT have two of their own children. JT reports that they were screened for VHL and are “thankfully negative”.

FT has had many surgeries for the removal of VHL-related cysts and tumors. One surgery was particularly consequential. In preparation for brain surgery FT was given an angiogram, which caused bleeding, which then caused a stroke. This stroke has left him permanently disabled and unable to work. FT now has trouble speaking, has permanent double-vision and needs to wear an eye patch. He has lost hearing in one ear and his jaw also doesn’t open properly and he cannot ingest food easily. JT told us that VHL has had a huge impact on FT’s ability to conduct day-to-day activities including work, exercise, and chores. Because of the disability incurred as a result of stroke, FT is no longer comfortable spending time with family and friends.

JT says that this disability is heartbreaking as FT was highly skilled, was entrepreneurial and ran his own business. Now he is unable to work with massive impacts on his mental health and happiness. JT reports that they now rely on financial support from FT’s elderly parents.

Experience with belzutifan

FT started using belzutifan in February 2022. JT reports that FT’s scans in November 2022 revealed a significant reduction in size of his kidney tumors and pancreatic cysts. Further, a cyst that was growing (rapidly) on his neck, behind his right ear has now stabilized, and appears to be reducing in size. And JT reports that an endolymphatic sac tumor (ELST) in JT’s brain has stopped growing.

JT says that FT is finding belzutifan to be tolerable, with minimal side effects. However, there is treatment-related fatigue and shortness of breath.

JT told us that belzutifan is a very effective treatment, with manageable side effects and that FT will continue to use belzutifan as long as it works.

JT did significant work to access belzutifan and went to her Member of Parliament in December 2021 to get help with FT’s Special Access Program application to Health Canada. The treatment is currently being reimbursed by the manufacturer’s patient support program.

RW (caregiver, date of Interview January 31, 2023.)

Patient is her husband: WW.

RW is a caregiver to her 51-year-old husband “WW”. RW has been with WW for 31 years living in northern BC and has seen his whole journey with VHL.

WW knew he had VHL in approximately 1997 as his older sisters and father had VHL, and when he went for an eye exam, the specialist observed that he “had a twisted nerve in the eye” which was suspected to be VHL-related. He has since confirmed the VHL diagnosis with genetic testing.

WW has had numerous kidney surgeries and brain surgeries. Some of these surgeries were done in Edmonton and some at National Institutes of Health (NIH) in Washington as part of a VHL study. Also noted were an additional fifteen (15) surgeries of which many were eye surgeries/cryotherapy for retinal hemangioblastomas.

RW reports that VHL has significantly impacted WW’s ability to work, travel, exercise and do household chores. RW reports that VHL has had moderate to high impact on WW’s ability to spend time with family and friends and fulfill family obligations. RW and WW believe that access to new treatments for VHL is very important. WW was a logger (machine operator) and worked for 26 years with one blind eye. But, as a result of additional tumors and burden of disease, he is now permanently out of the workforce.

RW and WW have seen significant financial impact as a result of VHL. They have seen reduced income now that WW is on long-term disability, but that ends in March 2023. RW reports that WW participating in the study at NIH had significant financial impact as their hotels were compensated at 50% when staying in Washington. When they go to Vancouver to see a VHL specialist, there are hotel costs, travel costs etc. related to staying in Vancouver. (They a 16-hour drive away).

30 members of WW’s extended family have VHL. Some are now blind. One nephew is paralyzed following brain surgery. About 6-8 members of his family are currently on belzutifan. Some are already reporting very positive results.

Experience with belzutifan

WW accessed belzutifan through a patient support program sponsored by the manufacturer and started treatment in August 2022. The belzutifan tablets are delivered to his home.

By November many of WW’s brain and kidney tumors have shrank significantly. RW believes that belzutifan will result in fewer surgeries for WW with a tremendous positive impact on his quality of life.

RW reports that WW finds the treatment to be quite tolerable, although his hemoglobin is now lower than optimal, he has some fatigue, and his oxygen is low.

RW reports that WW is hoping that belzutifan continues to shrink and/or stabilize his tumors so that he requires fewer surgeries and has a longer life expectancy. He is also hoping his offspring and extended family will benefit from this new treatment for VHL.

Other Patient and Caregiver Quotes

- I started having VHL surgeries at the age of 6 in 1965 & had my last open surgery at the age of 69 in 2021. Unfortunately the St Pauls Hospital in Vancouver, BC Tumor Board refused to do any more surgery due to my age & that they called me frail. This caused me to be bed ridden for the last 5 - 8 years due to disabling sciatica-like symptoms & stop driving my car due to pain pill consumption. I also had nausea & lost 50 pounds without trying. My Urologist, Dr. Michael Eng, found a Pancreas/Liver surgeon at Vancouver General Hospital, Dr. Peter Kim, who was willing to do surgery on my pancreas & let my Urologist also do an extra surgical procedure to scrape off one kidney tumor that he cannot reach with an RFA procedure. I no longer have disabling Sciatica pain. But unfortunately, because they waited too long, my kidney & pancreas tumors grew & became cancerous. I am now up & about & just have weakened core muscles & stiffness & tire easily due to 5 - 8 years of being bed ridden.*
- I have had 7 VHL open abdominal organ sparing surgeries to remove tumors on my pancreas, kidneys, adrenal glands & paraganglioma from between my vena cava & aorta. They also removed my spleen & gall bladder this last time. Each surgery I have to go under general anesthetic which increases my risk of anesthetic dementia as I age & the cutting of my core muscles, etc. repeatedly & affects my stamina & physical strength. I have slow growing Hemangioblastoma brain tumors which they are watching. I also hope the belzutifan will shrink or stop the growth of my brain tumors. I had to have 2 C-Sections as I was told I would "most likely expire if I went into labour", due to my adrenal & brain tumors in the 1970s. I hope belzutifan proves to shrink or stop the growth of these tumors also.*
- I have had so many CT scans to keep watch on my abdominal tumors over the years which gives me so much radiation exposure in my lifetime which is not healthy. (Every year for approximately 50 years) I have also had MIBG & PET Cat scan, and RFA (radio frequency ablation) procedures which adds to my radiation exposure.*

When we asked: **Please let us know how surgeries have impacted your ability to work or your quality of life, including spending time with loved ones.** 92 patients and caregivers provided commentary.

To give you an idea of what respondents were thinking, we put together this word cloud. The size and dark colouring of a word represents the frequency of its use, in the answers given.



- It is clear “time” is the most important thing.
- It is also a testament to the human condition how important “work” is to those surveyed.