CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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, or non-metastatic pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery

Sponsor: Merck Canada Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that belzutifan be reimbursed 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, or non-metastatic pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

pERC recognized the unmet need of patients with VHL disease-associated tumours, for which there are no other systemic therapies currently available. One phase II, single-arm, open-label trial (LITESPARK-004) demonstrated that treatment with belzutifan may result in a clinical benefit in objective response rate (ORR) for adult patients with VHL associated non-metastatic RCC (N=61), with or without CNS hemangioblastomas (N=50) and/or non-metastatic pNET (N=22), not requiring immediate surgery. At a median follow-up of 37.7 months, the objective response rate (ORR) assessed by independent review committee (IRC) was 63.9% (39/61) among patients with RCC, 44.0% (22/50) among those with CNS hemangioblastomas, and 90.9% (20/22) among those with pNET; the ORR was greater than the pre-specified alternative hypothesis of 30% and considered clinically meaningful.

Patients indicated there is a need for treatments that can improve their physical condition (e.g., decrease or stabilize the size of tumours, reduce pain, improve breathing), offer long-term stability or reduction of disease, avoid surgery, and improve health-related quality of life (HRQoL). pERC concluded that belzutifan meets some of the needs identified by patients, such as a meaningful ORR and durable tumour response as measured by duration of response (DOR). pERC considered that belzutifan could potentially meet additional needs, such as an opportunity to avoid surgery, although this is uncertain due to the single-arm design of the LITESPARK-004 trial and limitations of the indirect treatment comparison (ITC).

Using the sponsor submitted price for belzutifan and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for belzutifan was $360,193 per quality-adjusted life-year (QALY) gained compared with active surveillance for the VHL-RCC cohort. The ICERs were similar in the VHL-CNS hemangioblastoma and VHL-pNET subgroup cohorts. At this ICER, belzutifan is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for the indicated population. A price reduction is required for belzutifan to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY gained.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with VHL disease who require therapy for associated non-metastatic RCC, CNS hemangioblastomas, or non-metastatic pNET, not requiring immediate surgery.	pERC recognized the unmet need of patients with VHL disease-associated tumours. Evidence from the LITESPARK-004 trial demonstrated that treatment with belzutifan may have a beneficial effect in adult patients with VHL associated non-metastatic RCC, CNS hemangioblastoma, or non-metastatic pNET, not requiring immediate surgery.	In the LITESPARK-004 trial, patients were required to have VHL disease diagnosed on the basis of a germline VHL alteration. Patients with evidence of metastatic disease were excluded from the LITESPARK-004 trial, therefore the effects of belzutifan in patients with metastatic disease are unknown.
2. Patients must have good performance status.	The LITESPARK-004 trial included patients with an ECOG performance status of 0 or 1.	Good performance status should be as assessed by the treating clinician.
Discontinuation		
3. Belzutifan should be discontinued upon any of the following: 3.1. Clinical or radiographic disease progression 3.2. Intolerance of therapy	Treatment with belzutifan was discontinued upon disease progression or unacceptable adverse events in the LITESPARK-004 trial.	pERC noted that patients with VHL disease require complex care and should be managed by a multidisciplinary care team. The multidisciplinary care team should determine the frequency of clinical follow-up and imaging required. Patients who have experienced radiographic progression without clinical progression may continue to receive belzutifan if the patient is still deriving clinical benefit as assessed by the treating clinician.
Prescribing		
4. Belzutifan should be initiated by specialists with expertise in the management of VHL disease-associated tumours.	This is to ensure belzutifan is prescribed for the most appropriate patients, and that adverse effects are managed appropriately.	—
5. Belzutifan should be administered as a monotherapy.	Patients in the LITESPARK-004 trial were not permitted to receive anti-neoplastic agents, therefore the efficacy and safety of belzutifan used in combination with other anti-neoplastic therapies is unknown.	—
Pricing		
6. A reduction in price	The ICER for belzutifan is $360,193 per QALY gained for the VHL-RCC cohort when compared with active surveillance. A price reduction of 83% would be required for belzutifan to achieve an ICER of $50,000 per QALY gained compared to active surveillance.	—
Feasibility of adoption		

Reimbursement condition	Reason	Implementation guidance
7. The feasibility of adoption of belzutifan must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

CNS = central nervous system; ICER = incremental cost-effectiveness ratio; pNET = pancreatic neuroendocrine tumors; QALY = quality-adjusted life year; RCC = renal cell carcinoma; VHL = von Hippel-Lindau.

Discussion Points

- **Unmet need:** Due to the uncertainty associated with the design of the LITESPARK-004 trial, pERC deliberated on belzutifan considering the criteria for significant unmet need described in section 9.3.1 of the *Procedures for CADTH Reimbursement Reviews*. Considering the rarity and severity of VHL disease as well as the unmet need for a systemic treatment to avoid multiple surgeries and radiation, pERC concluded that although the available efficacy and safety evidence from the LITESPARK-004 trial is associated with uncertainty, belzutifan has the potential to reduce morbidity and/or mortality associated with the disease. Given the rarity of VHL disease, that active surveillance is currently the standard of care for patients with VHL associated non-metastatic tumours, and the morbidity associated with multiple surgeries and radiation required over the course of their lives, the small sample size and single-arm trial design adopted in the LITESPARK-004 trial was considered acceptable by pERC.
- **Patient needs:** pERC noted that patients indicated that the opportunity to avoid surgery is important to them, and expressed their willingness to tolerate side effects of a treatment that would allow avoidance of surgery to remove VHL associated cysts and tumours. Similarly, clinical experts indicated prolonging survival and avoiding morbid local therapies such as surgeries and radiation are among the most important treatment goals for patients with VHL disease. pERC noted that belzutifan may meet some of these needs such as an opportunity to avoid surgery, although it is uncertain due to the limitations of the evidence; time-to-event analyses for important outcomes such as time-to-surgery and progression-free survival are difficult to interpret in single-arm trials. pERC also noted that belzutifan appeared to be well-tolerated by patients with an acceptable harms profile in the LITESPARK-004 trial. In addition, patients placed importance on new treatments that could improve their quality of life. HRQoL was not assessed in the LITESPARK-004 trial, the VHL Natural History Study, nor the ITC. Findings from the VHL Natural History Study and the HRQoL survey submitted by the sponsor did not provide information on the efficacy or safety of belzutifan as standalone studies because patients included did not receive belzutifan. As such, the effect of belzutifan on HRQoL in patients with VHL disease is unknown.
- **Comparative evidence:** An ITC that used a real-world, retrospective cohort study as an external comparator for the LITESPARK-004 trial suggested that treatment with belzutifan may have a beneficial effect on time to RCC-related surgery compared to active surveillance in patients with VHL disease associated with non-metastatic RCC. However, the certainty of the ITC results was low due to methodological limitations and unaccounted differences in the populations between the studies, which could bias the findings. Although pERC considered that belzutifan is associated with an incremental benefit compared with active surveillance, they noted that the magnitude of benefit was associated with substantial uncertainty. As a result, the cost-effectiveness is associated with uncertainty. To mitigate the uncertainty associated with the comparative clinical evidence, a greater price reduction may be required. In the ITC analysis, the comparative efficacy of belzutifan versus active surveillance for VHL associated CNS hemangioblastoma and non-metastatic pNET was not assessed and is therefore unknown based on this evidence. In the economic evaluation, data for the CNS hemangioblastoma and non-metastatic pNET populations used were based on subgroups of the full RCC population from the LITESPARK-004 trial, for which there were very small patient numbers. As a result, pERC focused on the results of the VHL disease associated with non-metastatic RCC population when assessing the evidence in the economic evaluation.
- **Patient population:** pERC noted that the LITESPARK-004 trial population represents a narrower population than the proposed Health Canada indicated population, however according to clinical experts, results from the LITESPARK-004 trial may be generalized to patients with CNS hemangioblastoma and/or pNET without the presence of RCC.
- **Treatment duration:** pERC noted that since VHL is a life-long condition and patients could receive belzutifan for a long period of time, the long-term benefits and harms of belzutifan, as well as potential residual effects following discontinuation are gaps in the current evidence.

- **Embryo-fetal toxicity:** pERC noted that patients with VHL disease can have reproductive potential. Exposure to belzutifan during pregnancy can cause embryo-fetal harm. Patients who were pregnant were excluded from the LITESPARK-004 trial and treatment would be discontinued if a patient became pregnant during the study. pERC indicated that patients could temporarily stop treatment with belzutifan to become pregnant and restart treatment after pregnancy. pERC noted that there is a potential risk related to fertility. Fertility studies with belzutifan have not been conducted, thus the effect of belzutifan on fertility in people with reproductive potential is unknown. Family planning, the risks of embryo-fetal harm, and methods of contraception should be discussed with patients who may be impacted.
- **Ethical and equity considerations:** pERC discussed ethical and equity considerations related to belzutifan, including the substantial impact of VHL on patients' and families' quality of life and physical and mental health, the burden of life-long, active surveillance and multiple surgical and radiological interventions required for managing VHL, and the absence of disease modifying therapies for this rare disease. The committee also discussed the diagnostic and psychosocial challenges associated with the hereditary nature of VHL, including potentially distressing decision-making around the disclosure of genetic information to at-risk family members for a disease requiring burdensome surveillance and management and in the absence of a disease-modifying therapy or in the context of evidentiary uncertainty associated with belzutifan. The need for genetic counselling and enhanced mental health and community or social resources to support patient and family decision-making was also highlighted as a key ethical consideration. pERC also discussed the evidentiary uncertainty concerning the safety and efficacy of belzutifan, especially in the long-term, and how this uncertainty presented challenges for assessing its cost-effectiveness and impact on patients. The committee also discussed the need for conversations with patients about an acceptable balance of benefits and risks, and the need for robust and iterative informed consent (given the potentially life-long nature of the medication) and disclosure of uncertainty about the long-term safety, efficacy, and tolerability of belzutifan, including impact on fertility. The committee discussed how equitable access to belzutifan requires attending to potential geographic and diagnostic barriers to access, including for ongoing multi-disciplinary, specialist care and monitoring. They also discussed how belzutifan highlighted the challenges of funding decisions and assessments of opportunity costs for expensive drugs for rare diseases, as well as the need for better health information systems capacity and coordination of multi-disciplinary and ongoing treatment, monitoring and care for patients with VHL as a multi-systemic condition.

Background

VHL disease, which is an inherited, autosomal dominant neoplasia syndrome caused by a germline mutation and/or deletion of the VHL gene, is associated with a variety of neoplasms such as hemangioblastomas of the CNS and retina, renal cysts and clear cell RCC, pheochromocytomas, pNET, epididymal and broad ligament cystadenomas, and endolymphatic sac tumours. VHL disease affects 1 in 36,000 live births. Approximately 20% of the cases are caused by de novo mutations and hence do not have a family history of VHL. The prevalence is estimated to be 1 in 53,000 individuals. In Canada, the estimated number of cases is 727.

The diagnosis of VHL disease is typically established through genetic testing to identify a germline pathogenic variant in the VHL gene. People with VHL disease can have tumours involving multiple organs many times in their life and their symptoms will depend on the location and size of the tumours. Tumours associated with VHL disease have the potential to metastasize. Active surveillance until treatment is indicated is currently the standard approach for VHL disease associated tumours. The goal of active surveillance is to find and remove tumours as early as possible before they affect the patient's health. Surgical resection is indicated for tumours with high symptom burden or those carrying a high risk of organ dysfunction or metastasis. Certain tumors can be treated with radiation. However, treatments such as surgery and irradiation can be morbid. There is a need among patients and clinicians for a systemic treatment which could be effective in treating VHL disease while causing less harm.

Belzutifan has been approved by Health Canada for the treatment of adult patients with VHL disease who require therapy for associated non-metastatic RCC, CNS hemangioblastomas, or non-metastatic pNET, not requiring immediate surgery. Belzutifan is an antineoplastic agent. It is available as 40 mg tablets and the dosage recommended in the product monograph is 120 mg (three 40 mg tablets) administered orally once daily, with or without food.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of a phase II, single-arm, open-label trial in patients with VHL disease; an ITC; a real-world, retrospective, non-interventional cohort study; and a cross-sectional HRQoL survey
- patient perspectives gathered by 5 patient groups, the Canadian VHL Alliance, the Canadian Organization for Rare Disorders, Kidney Cancer Canada, Pancreatic Cancer Canada, and the Canadian Neuroendocrine Tumour Society
- input from public drug plans and cancer agencies that participate in the CADTH review process
- a panel of 3 clinical specialists with expertise diagnosing and treating adult patients with VHL disease who require therapy for associated non-metastatic RCC, CNS hemangioblastomas, or non-metastatic pNET, not requiring immediate surgery
- input from 2 clinician groups, including Ontario Health Cancer Care Ontario Genitourinary Cancer Drug Advisory Committee and 25 Canadian subspecialists involved in VHL care
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to belzutifan.

Stakeholder Perspectives

Patient Input

The Canadian VHL Alliance (CVHLA), The Canadian Organization for Rare Disorders (CORD), Kidney Cancer Canada, Pancreatic Cancer Canada, and the Canadian Neuroendocrine Tumour Society (CNETS) provided 1 joint input for the treatment of adult patients with VHL disease who require therapy for associated non-metastatic RCC, CNS hemangioblastomas, and non-metastatic pNET, not requiring immediate surgery. Patient input was gathered from online surveys and semi-structured telephone interviews among patients living with VHL and their caregivers in December 2022. In total, 123 responses were gathered (72 from patients and 51 from caregivers), and 19 patients had experience with belzutifan.

Patients and caregivers described their ongoing physical and psychological struggles due to VHL, such as dismissal or misdiagnosis for initial symptoms; not getting a diagnosis until they had an advanced stage resulting in a tumour affecting vision, hearing, and walking; discomfort, pain, interference with daily activities; difficulties in adhering to tumour screening guidelines, scheduling tests, traveling for tumour screenings; and out of pocket payment due to non-coverage by public healthcare or private insurance. Surgical resection was reported as the primary treatment for symptomatic lesions. The majority of 92 respondents described their experiences with surgeries as undergoing multiple surgeries on multiple sites, some with life-threatening risks and side effects. Out of 98 respondents, 18 (18.4%) reported having 10 or more surgeries, and the average number of surgeries reported was 5.3.

While evaluating the importance of outcomes of new treatments, patients from the survey placed importance on the need for a treatment that can improve their physical condition by decreasing or stabilizing the size of tumours (weighted average rating: 4.8 on a scale from 1 not important to 5 extremely important), improving quality of life (weighted average rating: 4.63 on a scale from 0 not important to 5 extremely important), offering long-term stability or reduction of disease (weighted average rating: 4.86 on a scale from 0 not important to 5 extremely important), and offering the opportunity to avoid surgery (weighted average rating: 4.9 on a scale from 0 not important to 5 extremely important).

The patient groups suggested to provide all VHL patients the access to belzutifan based on an individual informed decision between the treating physician and the patient and their family.

Clinician input

Input from clinical experts consulted by CADTH

The clinician input was provided by a panel of 3 clinical experts with expertise in treating VHL associated RCC, CNS hemangioblastoma, and pNET from across Canada.

The clinical experts noted that prolonging survival and improving quality of life are critical goals for patients with VHL associated non-metastatic RCC, CNS hemangioblastoma, and/or non-metastatic pNET. Current treatment paradigm for VHL disease involves genetic testing for VHL at diagnosis and active surveillance until treatment is indicated for associated tumours. Reactive treatments, such as surgery and radiation, can be morbid and are usually selected to respond to the conditions or symptoms developed. The clinical experts agreed that an effective systemic treatment would minimize the morbidity associated with surgical procedures in patients with VHL associated non-metastatic pNET and RCC, many of whom are younger. The clinical experts noted that belzutifan, if reimbursed, would be the first systemic treatment for VHL associated tumours, which would change the current treatment paradigm by helping patients delay or avoid the need for local therapies (e.g., surgery and radiation).

The clinical experts indicated that VHL is a rare disease and all patients with VHL might benefit from belzutifan. The clinical experts did not specify any subset of the patient population for whom is in the most need or identify any prognostic factors that might cause differential treatment effects. The clinical experts noted that prior to initiating treatment with belzutifan, genetic testing for diagnosing VHL should be required. The clinicians also noted that a genetic counselor should be involved in the diagnosis of VHL disease.

The clinical experts noted several situations in which belzutifan may be discontinued, including intolerable adverse events (e.g., becoming transfusion dependent due to anemia), clinical disease progression (e.g., worsening of symptoms). The clinical experts indicated that strict stopping criteria based on radiographic disease progression alone would not be reasonable if patients were still experiencing clinical benefit. The clinical experts noted that due to the rarity of the VHL disease, it is highly likely that only specialists working in large medical centers (e.g., tertiary referral centers, specialized referral center) in Canada may encounter patients with VHL. Thus, prescription may be limited to specialists (e.g., medical oncologist, neuro oncologists) working in these large centers.

Clinician group input

Clinician group input was received from Ontario Health Cancer Care Ontario (OH-CCO) Genitourinary Cancer Drug Advisory Committee (GU DAC) (7 clinicians), and a group of Canadian subspecialists involved in VHL care (25 clinicians).

The clinician groups agreed with the clinical experts consulted by CADTH that belzutifan, the first systemic therapy option for VHL disease approved in Canada, fulfills an important unmet need for the treatment of patients with VHL and represents a shift in the current treatment paradigm. They also generally agreed upon treatment goals, patient population, assessing response, treatment discontinuation criteria, and prescribing conditions.

While the clinical experts considered genetic testing to be a prerequisite for initiating treatment with belzutifan, neither clinician group indicated whether genetic testing for VHL mutation or deletion was required. The clinician group indicated that belzutifan should be discontinued if the patient is pregnant.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Implementation Issues	Response
Relevant Comparators	
There is one pivotal clinical study (LITESPARK-004): • A phase II open-label, single-arm, multicenter study • No comparator was involved • The drug plans had no issues as standard of care for VHL is routine active surveillance.	This is a comment from the drug plans to inform pERC deliberations.
The drug plans presented the following implementation issues regarding relevant comparators: • Exposure to belzutifan during pregnancy can cause embryo-fetal harm.	This is a comment from the drug plans to inform pERC deliberations.

Implementation Issues	Response
• Verify pregnancy status prior to the initiation of belzutifan. • Advise patients of these risks and the need for effective non-hormonal contraception. • Belzutifan can render some hormonal contraceptives ineffective.	
Considerations for Initiation of Therapy	
Should non-metastatic status be stated in the eligibility criteria?	pERC agreed with the clinical experts, who noted that non-metastatic status should be stated in the eligibility criteria for reimbursement because the data in the LITESPARK-004 trial were from patients with VHL associated non-metastatic tumours (i.e., the study excluded patients with evidence of metastatic disease). However, the clinical experts noted that CNS hemangioblastomas typically are not described as non-metastatic or metastatic.
Should pediatrics be eligible for belzutifan?	pERC noted that pediatric patients are outside of the scope of the Health Canada-approved indication, which is limited to adult patients with VHL disease. The clinical experts indicated they would like to expand the use of belzutifan in pediatrics but noted that the indication for belzutifan is for adult patients and the LITESPARK-004 trial restricted enrollment to adult patients. The clinical experts acknowledged that expanding belzutifan in pediatrics may not be feasible due to lack of research data in this population.
Should belzutifan be considered in patients with ECOG > 1?	The clinical experts preferred not to set requirements for ECOG performance status to initiate belzutifan because ECOG performance status could be unstable and subjective. The clinical experts indicated that in clinical practice, the clinician may determine that a patient with an ECOG performance status > 1 could benefit from belzutifan. pERC agreed that patients with good performance status are eligible for treatment with belzutifan.
Is belzutifan a lifelong therapy with time off only for surgical interventions while in the non-metastatic state?	The clinical experts were uncertain regarding how long patients would be on treatment with belzutifan. The clinical experts noted that the median follow-up time in the LITESPARK-004 trial at the time of this review was limited to 37.7 months. The clinical experts also noted that whether belzutifan becomes a lifelong therapy depended on how well and how long belzutifan can work to prevent disease progression. The clinical experts noted that a time limit should not be put on the use of belzutifan, and they would continue treatment with belzutifan until the patient experiences disease progression or unacceptable toxicity. pERC agreed with the clinical experts.
Considerations for discontinuation of therapy	
It is noted that patients may receive belzutifan on and off to allow for surgical interventions?	The clinical experts agreed that patients may receive belzutifan on and off to allow for surgical interventions.

Implementation Issues	Response
What are the discontinuation criteria for belzutifan?	The clinical experts noted the following situations in which belzutifan may be discontinued: • Intolerable side effects (e.g., becoming transfusion dependent due to anemia) • Clinical disease progression (e.g., worsening of symptoms) • Radiographic disease progression, although the clinical experts noted that they may continue treatment with belzutifan in some patients who have experienced radiographic progression without clinical progression, if the patient is still deriving clinical benefit in the opinion of the clinician pERC agreed with the clinical experts and noted that patients may have tumours at multiple sites. In a patient with tumours in multiple sites, pERC indicated that these patients may remain on treatment with belzutifan as long as they are still deriving clinical benefit in the opinion of the treating clinician. The clinical experts noted the patients who have remained in a stable status for a long time may make a personal decision to discontinue belzutifan and be actively monitored.
Considerations for prescribing of therapy	
Belzutifan is taken 120 mg orally daily	This is a comment from the drug plans to inform pERC deliberations.
Care provision issues	
Belzutifan is provided as a 40 mg tablet (120 mg starting daily dose); provided in bottles of 90 tablets. Dispensing will require discussion of reproductive risk to patients (all genders), contraception, and avoidance of pregnancy throughout therapy and for at least 1 week after last dose. Based on experience during the LITESPARK-004 Study, 82% of patients experienced a dose interruption. Additionally, 18% of patients had a dose reduction to 80 mg orally daily, and 6.6% of patients had a dose reduction to 40 mg orally daily. Additionally, 28% of patients discontinued therapy for reasons other than progressive disease. If reimbursed, drug wastage may occur should dose interruptions/discontinuations occur after a supply of belzutifan is dispensed.	This is a comment from the drug plans to inform pERC deliberations.

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; pNET = pancreatic neuroendocrine tumour; RCC = renal cell carcinoma; VHL = von Hippel-Lindau.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of study

One sponsor conducted phase II, single-arm, open-label trial (LITESPARK-004, N = 61) was identified from the systematic literature review (SLR) conducted by the sponsor. The primary objective of the LITESPARK-004 trial was to evaluate the efficacy of belzutifan (oral administration at the dose of 120 mg once daily in three 40-mg tablets until disease progression or unacceptable toxicity) for the treatment of VHL disease associated non-metastatic RCC as measured by ORR assessed by an IRC as per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1). Secondary objectives included the evaluation of the efficacy of belzutifan for the treatment of VHL disease associated non-RCC tumours (CNS hemangioblastoma and non-metastatic pNET), as well as the assessment of the safety and tolerability (including AEs of special interest; anemia, hypoxia, secondary primary malignancies, hepatic safety). In terms of efficacy endpoints, tumour response and durability of response were assessed by ORR and duration of response (DOR), respectively. Time-to-event outcomes, such as time to surgery (TTS), progression-free survival (PFS), time to response (TTR) were also reported. Additionally, the LITESPARK-004 trial also measured endpoints such as disease control rate (DCR), best overall response (BOR), linear growth rate (LGR), and number of patients who developed metastases. No inferential statistical analyses were carried out in the LITESPARK-004 trial due to the single-arm study design, and data were summarized using descriptive statistics. The LITESPARK-004 trial is ongoing, and the data submitted by the sponsor to support this reimbursement request is based on the data cut-off date of April 1, 2022, as of which, the median follow-up duration was 37.7 months (range: 4.2 to 46.1).

Participants eligible to be included in the LITESPARK-004 trial were required to be at least 18 years of age, diagnosed with VHL disease based on a germline VHL alteration, and had at least 1 measurable RCC. Eligible patients could have other VHL disease associated non-RCC tumours such as CNS hemangioblastoma and pNET. Patients who had an immediate need for surgical intervention for tumour treatment or evidence of metastatic disease were excluded. Efficacy results for RCC came from the total study population (n = 61), while efficacy results for CNS hemangioblastoma (n = 50) and pNET (n = 22) were from subsets of the total study population. At baseline, for the total study population (i.e., patients with RCC), the median age was 41.0 years (range: 19.0 to 66.0) with the majority being white (90.2%, 55/61), and the median age at time of VHL disease diagnosis was 32.0 years (range: 4.0 to 66.0). Characteristics were similar for the subpopulations of patients with CNS hemangioblastoma and pNET.

Efficacy Results

The efficacy results are from the April 1, 2022 data cut-off date.

Time to surgery (TTS)

Median TTS was not reached for patients with VHL disease associated non-metastatic RCC, CNS hemangioblastoma, or non-metastatic pNET at the data cut-off date. Seven (11.5%, 7/61) patients with RCC, 1 patient (2.0%, 1/51) with CNS hemangioblastoma, and none of the patients with pNET had surgery during the follow-up period.

Progression-free survival (PFS)

The independent review committee (IRC)-assessed median PFS (95% confidence interval [CI]) was 39.2 months (38.5 to not evaluable) for patients with VHL disease associated non-metastatic RCC. Median PFS was not reached for patients with VHL disease associated CNS hemangioblastoma and those with non-metastatic pNET at the data cut-off date.

IRC-assessed results showed that among 61 patients with RCC at baseline, 11 (18.0%) had events (i.e., progressive disease, death), and 50 (82%) patients were censored mostly due to no progression at the time of data cut-off or before end of treatment (43, 70.5%).

IRC-assessed results showed that among 50 patients with CNS hemangioblastoma at baseline, 11 (22.0%) had events (i.e., progressive disease, death), and 39 (78%) patients were censored (in which 34 [68%] were due to no progression at the time of data cut-off).

All of the 22 patients with pNET were censored due to no progression at the time of data cut-off.

Objective response rate (ORR)

At a median follow-up of 37.7 months, the IRC-assessed percentage of patients who had a complete response (CR) or partial response (PR) to belzutifan was 63.9% (39/61) among those with VHL associated non-metastatic RCC, 44% (22/50) among those with VHL associated CNS hemangioblastomas, and 90.9% (20/22) among those with VHL associated non-metastatic pNET.

Duration of response (DOR)

IRC-assessed median DOR (95% CI) was not reached for responders with VHL disease associated non-metastatic RCC, CNS hemangioblastoma, or non-metastatic pNET at the data cut-off date. For patients with RCC, 74.4% (29/39) of responders had a DOR ≥ 18 months, 56.4 % (22/39) had a DOR ≥ 24 months, and 25.6% (10/39) had a DOR ≥ 30 months. For patients with CNS hemangioblastoma, 63.6% (14/22) of responders had a DOR ≥ 18 months, 59.1 % (13/22) had a DOR ≥ 24 months, and 54.5% (12/22) had a DOR ≥ 30 months. For patients with pNET, 95.0% (19/20) of responders had a DOR ≥ 18 months, 75.0% (15/20) had a DOR ≥ 24 months, and 40.0% (8/20) had a DOR ≥ 30 months.

Among 39 RCC patients with confirmed response, 32 (82.1%) were censored due to no progression at the time of data cut-off or before end of treatment. Out of 22 patients with CNS hemangioblastoma who showed confirmed response, 17 were censored due to no progression at the time of data cut-off or before end of treatment. All 20 patients with pNET who showed confirmed response had no progression at the time of data cut-off.

Harms Results

Adverse events (AEs)

Treatment-emergent adverse events (TEAEs) were reported in all 61 (100%) patients in the LITESPARK-004 trial. The most commonly reported TEAE was anemia (90.2%), followed by fatigue (73.8%), headache (47.5%), dizziness (45.9%), and nausea (39.3%).

Serious adverse events (SAEs)

SAEs were reported in 18 (29.3%) patients.

Withdrawals due to AEs

Treatment discontinuation due to TEAEs was reported in 4 patients, 2 (i.e., dizziness, intracranial hemorrhage) of which were drug related.

Mortality

Two patients died during the study due to acute toxic effects of fentanyl and suicide, respectively.

Notable harms

As of the data cut-off, 90.2% (55/61) patients had 229 episodes of anemia. The average number of episodes of anemia for each patient was 4.2. One (1.6%) and 2 (3.3%) patients developed hypoxia and secondary primary malignancies, respectively. None of the participants had drug-induced liver injury.

Critical Appraisal

Internal Validity

The LITESPARK-004 trial was a phase II, single-arm, open-label clinical trial. Given the rarity of the VHL disease and that active surveillance is the current standard of care for patients with VHL associated non-metastatic tumours, the single-arm design and small sample size was considered appropriate from the regulatory perspective to assess the efficacy and safety of belzutifan. However, the

absence of an internal comparison group in the single-arm LITESPARK-004 trial hampered the causality establishment of the efficacy or safety outcomes observed in patients.

The LITESPARK-004 trial explicitly defined the hypothesis (i.e., a null hypothesis of an ORR of 15% or lower with an alternate hypothesis of ORR of 30% or higher), which was considered clinically meaningful by the clinical experts consulted by CADTH. The selection of ORR (defined as sum of CR and PR per RECIST v1.1) to measure antitumour activity and DOR (i.e., duration of response in patients with CR or PR) to determine the durability of tumour response were appropriate. Additional time-to-event endpoints (i.e., TTS and PFS) were employed in the LITESPARK-004 trial, which were considered by the clinical experts as critical outcomes to assess the efficacy of belzutifan. However, RCTs are preferred over single-arm studies for time-to-event endpoints such as PFS due to their sensitivity to baseline differences in patient, disease, and other clinical characteristics, and results interpretation without a randomized reference could be problematic.[15-17] The LITESPARK-004 trial also involved outcomes pre- and post- treatment with belzutifan (i.e., change in LGR) to demonstrate the efficacy of belzutifan. However, without formal statistical analysis, the role of chance could not be ruled out. With respect to outcome measurement, in addition to study investigators, an IRC was also involved to assess radiographic outcomes to reduce the risk of bias in measurement of the outcome for most of the efficacy endpoints in patients with VHL associated non-metastatic RCC and those with VHL associated CNS hemangioblastoma.

Altogether, due to major limitations such as lack of comparison groups and lack of formal inferential statistical analyses, no definitive conclusions could be drawn from the LITESPARK-004 trial with respective to the efficacy and safety of belzutifan in patients with VHL associated non-metastatic RCC, CNS hemangioblastoma, or non-metastatic pNET, all of whom did not require immediate surgery.

External Validity

All participants in the LITESPARK-004 trial were required to have at least one RCC. Therefore, the LITESPARK-004 trial may not reflect results for participants with only CNS hemangioblastomas and/or pNETs. However, this was not considered a serious generalizability issue by the clinical experts consulted by CADTH. According to the clinical experts, the inclusion and exclusion criteria of the LITESPARK-004 trial in general were aligned with selection criteria in the Canadian settings when identifying suitable candidates for belzutifan. However, the clinical experts noted that the requirement for patients being of Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 might not be necessary in clinical practice to initiate belzutifan because they indicated ECOG status could be unstable and subjective. There were no study sites in Canada as the LITESPARK-004 trial was conducted in Denmark, France, United Kingdom, and the United States. Over 90% of the patients in LITESPARK-004 were white, which is not representative of the racial profile in the Canadian patient population according to the clinical experts. The dosing and administration of belzutifan in the LITESPARK-004 trial were consistent with the product monograph. The clinical experts commented that concomitant medications/procedures in the LITESPARK-004 trial were also appropriate and commonly used in the Canadian settings. The outcomes TTS, PFS, ORR, and DOR were commonly used in clinical trials of anticancer therapy and relevant to clinical practice, as per the clinical experts. These outcomes are also important to patients, who indicated they want treatments that offer the opportunity to avoid surgery, decrease or stabilize the size of tumours, and result in long-term stability or reduction of disease. However, LGR was not commonly adopted in clinical practice and may not correlate with clinical benefit. The clinical expert specializing in CNS hemangioblastoma noted that in clinical practice, RANO criteria is adopted instead of RECIST v1.1 to assess tumour response in patients with CNS hemangioblastoma. The LITESPARK-004 trial did not assess some outcomes that are important to patients such as symptoms and HRQoL.

Indirect Comparisons

Description of study

A sponsor conducted indirect treatment comparison (ITC) was submitted to supplement the absence of comparative evidence of belzutifan for the treatment of adult patients with VHL disease in the LITESPARK-004 trial. The ITC compared a real-world, retrospective, non-interventional cohort study of existing medical records of VHL patients managed and treated at the NCI in the United States or Canada (the VHL Natural History Study) with the LITESPARK-004 trial. Patients with VHL associated RCC from the VHL Natural History Study were reweighted to match the distribution of key baseline characteristics among patients with VHL associated RCC in LITESPARK-004 and compared using the matching-adjusted indirect comparison (MAIC) method. The comparative treatment was active surveillance. The primary and only outcome assessed was time-to-RCC related surgery.

Efficacy Results

The weekly exponential rate of RCC surgery was estimated at 0.00487 (standard error [SE]: 0.00034) in the matched Natural History Study sample versus 0.00071 (SE: 0.0003) in the LITESPARK-004 population.

Critical Appraisal

Findings from the sponsor conducted ITC, which used the VHL Natural History Study to provide an external comparator for the LITESPARK-004 trial, was considered of high uncertainty. Although the estimated decrease in rate of surgeries in the LITESPARK-004 trial relative to the VHL Natural History Study was large, several major limitations decreased CADTH's confidence in the results. First, the selection criteria that informed the VHL Natural History Study subcohort used in the ITC was intended to match with those from the LITESPARK-004 cohort but did not include some key criteria. Specifically, the Natural History Study cohort did not include restrictions on ECOG scores of 0 or 1; this difference incurs a risk of bias of the effectiveness that may favour belzutifan. Second, it was difficult to assess the degree of heterogeneity between the included studies based on the sponsor-provided technical report since reporting of study design and patient characteristics was limited. It is likely that the underlying assumption of the unanchored MAIC, that all potential prognostic and effect modifying factors were balanced across groups, was violated which would result in a high risk of confounding. Third, the outcome definition of RCC surgery within the Natural History Study cohort is subject to potential measurement error. Specifically, the clinical experts indicated that renography and cyst removal, are not definitive surgical interventions for management of RCC, although these were considered an RCC surgery outcome in the VHL Natural History Study. The magnitude of bias due to measurement error is unknown, but may overestimate the estimated relative rate of RCC surgeries in favour of belzutifan. Finally, the analysis did not provide information specific to VHL associated CNS hemangioblastoma and pNET populations.

Studies Addressing Gaps in the Pivotal and RCT Evidence

The sponsor submitted the VHL Natural History Study[39] to address the gap of no published clinical trial or observational data on the efficacy outcomes of the standard of care, which is active surveillance. This study provided the active surveillance efficacy data used for the ITC. The sponsor also provided a cross-sectional HRQoL survey[41] to address the gap of the lack of HRQoL or utility values, which is summarized and critically appraised in Appendix 1. This study assessed the impact of VHL disease on HRQoL as measured using the EQ-5D in patients with RCC, CNS hemangioblastoma, or pNET. A total of 220 patients completed the survey. Overall, patients with VHL associated tumours had a mean EQ-5D score of 0.771. Patients who participated in this study were not treated with belzutifan, therefore this study does not provide information related to the effect of treatment with belzutifan on the HRQoL of patients with VHL disease.

VHL Natural History Study

Description of Study

The VHL Natural History Study[39], a retrospective real-world cohort study of growth kinetics and surgical patterns in patients with VHL disease and associated renal solid tumours, was conducted using data registered by the National Cancer Institute (NCI) in a Hereditary Database of patients with VHL syndrome. The Primary Study Population consisted of US and Canadian patients treated at the NCI with confirmed VHL syndrome and ≥ 1 renal solid tumour with available measurement(s) during the study period (July 31, 2004, to June 30, 2020). Additional criteria were applied in an attempt to more closely match the study population to the one enrolled in the LITESPARK-004 trial.

Of 776 VHL patients in the NCI hereditary database, a total of 308 patients with at least one solid renal tumour met the eligibility criteria and were included in the Primary Study Population. After applying additional eligibility criteria focusing on the tumour growth rate assessment, 247 patients (80.2%) were included in the Trial Population Subgroup.

Subgroups of 131 patients and 114 patients in the Primary Study Population and the Trial Population Subgroup, respectively, had ≥ 3 serial measurements for at least one solid renal tumour during the study period that qualified them for inclusion in the LGR Analysis Subgroups to address the primary research objective.

Efficacy Results

LGR

The median tumour-level LGR for the Primary Study Population and Trial Population Subgroup was 0.38 cm/year (interquartile range [IQR]: 0.30 to 0.49) and 0.37 cm/year (IQR: 0.29 to 0.47]), respectively.

Frequency and type of tumour reduction procedures

Of the 308 patients in the Primary Study Population, 232 (75.3%) patients had at least 1 renal solid tumour reduction procedure during the study period including 225 (73.1%) patients with surgical procedures (96% of which were partial nephrectomies), 16 (5.2%) patients with ablation procedures, and 1 (0.3%) patient who received a radiation procedure. In the Trial Population Subgroup, 184 (74.5%) patients underwent at least 1 renal solid tumour reduction procedure. The median number of tumour reduction procedures per patient in the Trial Population Subgroup was 2 (range: 1 to 9).

Time to tumour reduction procedures

The 1-year, 2-year, 5-year, and 7-year intervention free survival probabilities for the first tumour reduction procedure were 79.0%, 69.9%, 38.3%, and 26.4%, respectively, for the Trial Population Subgroup. The median time to first tumour reduction procedure was 44.2 months (95% CI: 35.74 to 49.51) in the Trial Population Subgroup.

Harm Results

Of the 217 (70.5%) patients in the Primary Study Population with at least 1 partial nephrectomy, 413 partial nephrectomies were performed during follow-up, 124 (30.0%) of which were associated with complications. The median estimated blood loss, assessed among all surgical procedure types, was 1.5 L (IQR: 0.6 to 2.6). Two (0.9%) patients in the Primary Study Population with at least ≥ 1 renal tumour reduction procedure conducted at the NIH died within 30 days of the procedure (1 nephrectomy and 1 biopsy).

Critical Appraisal

Internal Validity

This real-world retrospective cohort study did not evaluate the effect of belzutifan and did not provide evidence about the efficacy of the treatment. There appears to be no a priori protocol for the analyses presented. The study was conducted using data registered by the NCI in a Hereditary Database of patients with VHL syndrome, but how these data were located (e.g., search methods) or selected is not specified.

Some of the limitations of this study were high level of missing data for some variables; unavailability of longitudinal measures of tumour growth for all tumours in a systematic manner (i.e., differences may have arisen due to variation in measurement across observers), since the measures were extracted from the registry directly; incomplete documentation of metastasis; and the possibility of misclassification. There is also a possibility of loss to follow-up of patients (i.e., left the registry), but no information was provided regarding this. Attempts were made to ensure that the Trial Population Subgroup would be similar to the population of the LITESPARK-004 trial, based on the additional criteria that were applied. However, several criteria in the Natural History Study cohort are approximate to those of the pivotal trial due to insufficient access to information within the database. While demographics and clinical characteristics were similar for patients in the Trial Population Subgroup and patients in the LGR Analysis Subgroups, many demographic characteristics (i.e., race/ethnicity and ECOG performance status) were not reported in the Natural History Study report. One of the exclusion criteria was receiving systemic oncologic therapy or investigational therapy within 30 days on or prior to the Patient-Level Index Date. However, no specific information was given about the type of systemic or investigational therapy. Moreover, this exclusion criteria might have led to exclude patients with better prognosis, thus affecting the results for the Trial Population Subgroup.

External Validity

This study includes patients managed and treated at the NCI only. This may impact the overall generalizability of the study, as this may not be representative of all patients with VHL in Canada that fall within the Health Canada approved indication. While this study presented data for renal tumours, patients included in the study also had other tumours associated with VHL. However, there was no

additional information provided for these tumours, which might have excluded some important clinical outcomes associated with VHL syndrome. Since the indication under review includes non-metastatic pNETs and CNS hemangioblastomas in addition to non-metastatic RCC, the unavailability of data related to these two tumours represents a gap in the evidence provided by this study. The authors of this study noted the potential risk of losing substantial sample size due to the eligibility criteria of recruiting patients with ≥3 serial measurements for the assessment of tumour growth rate patterns.

Ethical Considerations

Patient group, clinician group, clinical expert, and drug program input gathered in the course of this CADTH review, as well as relevant literatures, were reviewed to identify ethical considerations relevant to the use of belzutifan for the treatment of adult patients with VHL disease who require therapy for associated non-metastatic RCC, CNS hemangioblastomas, or non-metastatic pNET, not requiring immediate surgery.

- Ethical considerations in the context of VHL highlighted the significant physical and psychosocial burden of the disease on patients, families, and caregivers; diagnostic and psychosocial challenges associated with the hereditary nature of the disease; and the absence of systemic, disease-modifying therapies.
- Clinical trial evidence indicated that there is presently evidentiary uncertainty concerning the safety and efficacy of belzutifan, especially in the long-term; this uncertainty limits assessment of clinical benefits and harms associated with treatment as well as pharmacoeconomic assessment of cost-effectiveness.
- The use of belzutifan presents potential risks for patients, including common risks of anemia, hypoxia, and embryo-fetal toxicity. Patients and clinicians expressed a willingness to undertake some risks for the potential benefit of a systemic therapy that could delay disease progression given the burden associated with VHL-associated tumors and local treatments, as well as the absence of alternative disease-modifying therapies. Robust informed consent processes are required to disclose risks of adverse events and evidentiary uncertainty about the long-term safety, efficacy, and tolerability of belzutifan, including impact on fertility. Equitable access to belzutifan requires attending to potential geographic and diagnostic barriers to access, including for ongoing specialist care and monitoring.
- Ethical considerations for health systems related to the implementation of belzutifan highlighted the challenges of funding decisions and assessments of opportunity costs for expensive drugs for rare diseases, the need for better coordination of multi-disciplinary and ongoing treatment, monitoring, and care for VHL, and improved health information systems capacity.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov Model
Target population	Adult patients (18 years or older) with VHL-associated RCC, CNS Hb, or pNET, who require therapy and do not require immediate surgery. The three cohorts were modelled independently.
Treatment	Belzutifan
Dose Regimen	120 mg (three 40 mg tablets) administrated orally once daily, with or without food, until unacceptable toxicity or disease progression.
Submitted Price	$213.33 per 40 mg tablet
Treatment Cost	$17,920 per 28 days
Comparator	Active surveillance
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (59 years)
Key data sources	Patient-level data from the LITESPARK-004 trial of belzutifan and a real-world natural history study of VHL-associated RCC patients (VHL Natural History Study)

Component	Description
Key limitations	• Long-term clinical efficacy of belzutifan in patients with VHL-associated non-metastatic RCC, CNS Hb, or non-metastatic pNET, is unknown. The median TTS in the LITESPARK-004 trial was not reached in any cohort. The sponsor predicted a survival benefit for belzutifan compared with active surveillance, despite the absence of robust evidence to support an OS benefit for belzutifan. • There is uncertainty in the relative efficacy of belzutifan compared with active surveillance due to limitations in assessing the degree of heterogeneity between the populations in the LITESPARK-004 and VHL Natural History Study. Clinical expert feedback received by CADTH noted that despite the methodologic limitations, belzutifan appears to have a promising tumour response compared to their experience with the natural history of the disease; however, the magnitude of benefit associated with belzutifan is unknown. • In the sponsor's base case, the ToT for patients receiving belzutifan was informed by the Weibull curve fitted to the time to treatment discontinuation data from LITESPARK-004. Given the follow-up period for the LITESPARK-004 trial (median 37.8 months), the sponsor's ToT for patients receiving belzutifan is associated with uncertainty. Clinical expert feedback received by CADTH noted that the Weibull extrapolation likely overestimates the ToT expected for patients receiving belzutifan in Canadian clinical practice. • The sponsor assumed that upon belzutifan treatment discontinuation, a patient's probability of requiring surgery, experiencing metastatic disease, or dying would linearly converge to active surveillance over [redacted] years. Feedback from clinical experts noted that patients who received belzutifan may achieve some residual benefit after treatment discontinuation; however, the sponsor's assumption of [redacted] years was likely overestimated. Without post-discontinuation efficacy data there is significant uncertainty in how tumours may grow after belzutifan discontinuation. • CADTH also identified several other limitations that may bias the results in favour of belzutifan including: RDI for belzutifan based on utilization in the LITESPARK-004 trial; inclusion of belzutifan genetic pricing after 10 years; and incorporating caregiver disutility. • Poor modelling practices were employed as the sponsor's model included numerous IFERROR statements that limit a thorough auditing of the model given the lack of transparency.
CADTH reanalysis results	• CADTH conducted a base case analysis that included: removal of belzutifan residual benefit after treatment discontinuation during the post-trial period; removal of caregiver disutility; and, removal of belzutifan trial RDI and generic costing assumptions. The CADTH base case focused on the VHL-RCC population. In order to be eligible for the LITESPARK-004 trial, all patients had to have RCC; therefore, the CNS Hb and pNET populations are informed by a small subset of patients captured in the broader RCC cohort. • The CADTH base case analysis reported ICERs for belzutifan versus active surveillance of $360,193 per QALY gained for the VHL-RCC population. A price reduction of approximately 83% is required for belzutifan to be considered cost-effectiveness at a $50,000 per QALY WTP threshold. The ICERs and price reductions for belzutifan were similar in the VHL-CNS Hb ($368,886 per QALY gained) and VHL-pNET ($314,661 per QALY gained) subgroups. • The cost-effectiveness of belzutifan in patients with VHL-associated CNS or pNETs who do not have RCC is unknown as the LITESPARK-004 trial population represents a narrower population than the proposed Health Canada indicated population. Should RCC have no impact on other tumour types, then the subgroup analyses conducted may be generalized to patients with only VHL-associated CNS or pNETs.

CNS = central nervous system, Hb = hemangioblastomas, ICER = incremental cost-effectiveness ratio, LY = life-year, NOC = Notice of Compliance, pNET = pancreatic neuroendocrine tumours, QALY= quality-adjusted life-year, RCC = renal cell carcinoma, RDI = relative dose intensity, TTS = time to surgery, ToT = time on treatment, VHL = von Hippel-Lindau, WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the submitted model was unnecessarily complex and difficult to validate, the number of patients eligible for treatment with belzutifan is uncertain and may be underestimated, the market shares for belzutifan were likely underestimated, the time on treatment for patients receiving belzutifan is uncertain, and the use of relative dose intensity to estimate drug costs is inappropriate.

Due to the lack of face validity and overly complex structure of the sponsor's model, CADTH was unable to undertake a base case reanalysis using the sponsor's model. CADTH used the sponsor's epidemiologic approach to determine the base number of patients in Year 1 based on the sponsor's estimates of population growth, VHL prevalence, diagnosis rate, tumour type, eligibility to start treatment (e.g., do not require immediate surgery), and public drug coverage rate. Eligible patients in Years 2 and 3 were added using Canadian population growth and the same variables as above. The CADTH reanalysis used median time on treatment, and revised estimates of the diagnosis rate of VHL disease, patients eligible to start treatment, the public coverage rate, and relative dose intensity. Based on the CADTH reanalysis, the three-year budget impact to the public drug plans of introducing belzutifan for the treatment of adults with VHL disease who require therapy for associated non-metastatic RCC, CNS Hb, or non-metastatic pNET, not requiring immediate surgery is expected to be $52,864,610 (Year 1: $13,881,930; Year 2: $17,588,769; Year 3: $21,393,912).

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: July 12, 2023

Regrets:

One expert committee member did not attend.

Conflicts of interest:

None.