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Reimbursement Recommendation

Belzutifan (Welireg)

Indication: For the treatment of adult patients with advanced renal cell carcinoma following a programmed death receptor-1 or programmed death-ligand 1 inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Welireg?

Canada's Drug Agency (CDA-AMC) recommends that Welireg be reimbursed by public drug plans for the treatment of adult patients with advanced renal cell carcinoma (RCC) following treatment with a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Welireg should only be covered to treat adult patients with RCC that either cannot be removed by surgery (unresectable) or has started to spread nearby (locally advanced) or to other parts of the body (metastatic). Patients should have a diagnosis of clear cell RCC, a type of RCC in which the cancer cells look clear under a microscope. In addition, patients must have experienced disease progression despite treatment with a PD-1 or PD-L1 inhibitor and VEGF-TKI received in sequence or together. Patients should have a good performance status.

What Are the Conditions for Reimbursement?

Welireg should only be reimbursed if it is prescribed by clinicians with expertise in treating advanced RCC and if the cost of Welireg is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Welireg delayed disease progression and prolonged tumour response compared to everolimus.
- Based on the CDA-AMC assessment of the health economic evidence, Welireg does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Welireg meets patients' needs because it improves disease control and may maintain health-related quality of life, delays disease progression, and offers an additional treatment option compared to everolimus.
- Based on public list prices, Welireg is estimated to cost the public drug plans approximately $12.6 million over the next 3 years. However, the actual budget impact is uncertain and will depend on the uptake of Welireg in the third or fourth line of therapy.

Summary

Additional Information

What Is RCC?

RCC is the most common type of kidney cancer, accounting for approximately 90% of all cases. It begins in the lining of the tiny tubes of the kidney, which help to filter blood and produce urine. People with advanced or metastatic RCC have cancer that has spread to other organs or body parts, such as the bones, lungs, liver, and brain. In 2024, the estimated number of new cases of kidney cancer was 9,000 cases in Canada.

Unmet Needs in RCC

Despite current treatment options, long-term survival and cure are still rare in adult patients with advanced RCC, especially in the second-line setting and beyond. Less than 10% of patients with metastatic disease survive for 5 years or longer. Treatment options for third- or later-line settings for advanced RCC remain limited, with no established standard treatments for fourth-line advanced RCC. There is an unmet need for effective and safe therapy options.

How Much Does Welireg Cost?

Treatment with Welireg is expected to cost approximately $17,920 per patient per 28-day cycle.

Recommendation

The Canada's Drug Agency (CDA-AMC) pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that belzutifan be reimbursed for the treatment of adult patients with advanced renal cell carcinoma (RCC) following treatment with a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (RCT) (LITESPARK-005; N = 746) demonstrated that treatment with belzutifan resulted in a moderate clinical benefit in adults with advanced RCC that had progressed after prior PD-1 or PD-L1 inhibitor and VEGF-TKI therapies. The LITESPARK-005 trial demonstrated that treatment with belzutifan resulted in statistically significant and clinically meaningful improvements in progression-free survival (PFS) compared with everolimus after a median follow-up time of 13.5 months (hazard ratio [HR] = 0.75; 95% confidence interval [CI], 0.63 to 0.90). Two-year PFS rates with a median follow-up time of 19.6 months were 17.5% (95% CI, 13.7% to 21.7%) for belzutifan and 4.1% (95% CI, 2.0% to 7.2%) for everolimus. Belzutifan also demonstrated statistically significant improvements in objective response rate (ORR) compared with everolimus (percentage difference [belzutifan minus everolimus] = 18.4%; 95% CI, 14.0% to 23.2%). pERC noted durable responses in patients treated with belzutifan; the median duration of response was 19.3 months and 13.7 months in the belzutifan and everolimus groups, respectively, at a median follow-up time of 19.6 months. pERC considered that belzutifan likely results in little to no difference in OS compared with everolimus. The interpretation of OS was limited by imprecision in the estimates (wide CIs that crossed the null). Although descriptive in nature and limited by low completion rates, treatment with belzutifan did not suggest a detriment in health-related quality of life (HRQoL) from baseline to week 17. The committee considered the safety profile of belzutifan to be manageable but noted the risk of anemia and hypoxia which require adequate monitoring and appropriate dose adjustment.

The clinical experts anticipated that belzutifan and axitinib would have similar efficacy and tolerability based on how these drugs perform in clinical practice. However, there was no evidence comparing belzutifan with other relevant comparators, such as axitinib or cabozantinib.

Patients identified a need for effective treatment options that improve quality of life and disease control, provide prolonged tumour response and durable remission, have fewer adverse events (AEs), and offer an additional treatment option. pERC concluded that, compared to everolimus, belzutifan met some patient needs because it improves disease control and may maintain HRQoL, delay disease progression, and offer an additional treatment option, although the impact of belzutifan relative to other comparators remains uncertain.

Using the sponsor-submitted price for belzutifan and publicly listed prices for all other drugs, the incremental cost-effectiveness ratio (ICER) for belzutifan was $731,313 per quality-adjusted life-year (QALY) gained

compared with everolimus and $664,048 per QALY compared with axitinib. At these ICERs, belzutifan is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for the treatment of adult patients with advanced RCC following a PD-1 or PD-L1 inhibitor and a VEGF-TKI. A price reduction is required for belzutifan to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with belzutifan should be reimbursed in adult patients with unresectable, locally advanced, or metastatic RCC who meet all the following criteria: 1.1. have clear cell RCC histology 1.2. have experienced disease progression on or after having received systemic treatment for locally advanced or metastatic RCC with PD-1 or PD-L1 checkpoint inhibitors and VEGF-TKI therapy in sequence or in combination.	Evidence from the LITESPARK-005 trial showed that treatment with belzutifan compared to everolimus resulted in clinical benefit in patients with these characteristics.	pERC agreed with the clinical experts consulted by CDA-AMC that histologic subtypes outside of clear cell RCC should not be eligible for belzutifan at this time. Belzutifan selectively targets a pathway (HIF-2alpha) predominantly relevant to clear cell RCC. The comparative efficacy and safety of belzutifan compared to currently available VEGF-TKI therapies in second line is unknown. Clinical experts suggested that belzutifan may be used as a last-line therapy in third- or fourth-line settings.
2. Patients should have good performance status.	Patients with a KPS of ≥ 70 were included in the LITESPARK-005 trial.	Treating patients with a KPS of < 70 may be at the discretion of the treating clinician.
3. Patients must not have any of the following: 3.1. active central nervous system metastases 3.2. hypoxia as defined by pulse oximeter reading (< 92% at rest).	The LITESPARK-005 trial excluded patients with active CNS metastases and hypoxia. There is no evidence to suggest these patients will benefit from treatment with belzutifan.	Patients with treated or stable CNS metastases should be eligible for treatment.
Discontinuation		
4. Reimbursement of belzutifan should continue until disease progression or unacceptable toxicity, whichever occurs first.	Patients in the LITESPARK-005 trial discontinued treatment upon disease progression or unacceptable toxicity. Continuation of study treatment after confirmed disease progression was allowed in the LITESPARK-005 trial if the investigator believed the patient was deriving clinical benefit.	pERC agreed that treatment with belzutifan could be continued until clinically meaningful progression occurs based on the judgment of the treating clinician.
Prescribing		
5. Belzutifan should be prescribed by a clinician with expertise in treating advanced RCC.	This is meant to ensure that belzutifan is prescribed for appropriate patients and that adverse effects are managed in an optimal and timely manner.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
6. A reduction in price.	The ICER for belzutifan is $731,313 compared with everolimus and $664,048 compared with axitinib. A price reduction of at least 74% to 82% would be required for belzutifan to achieve an ICER of $50,000 per QALY compared to these oral comparators.	—
Feasibility of adoption		
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 the CDA-AMC estimates.	—

CDA-AMC = Canada's Drug Agency; CNS = central nervous system; ICER = incremental cost-effectiveness ratio; KPS = Karnofsky Performance Status; PD-1 = programmed death receptor-1; PD-L1 = programmed death-ligand 1; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

Discussion Points

- **Unmet need:** Input from patient groups and clinicians highlighted that locally advanced or metastatic RCC is an aggressive disease with poor prognosis. Despite current treatment options, long-term survival and cure are still rare, particularly in the second-line setting and beyond, with less than 10% of patients with metastatic disease surviving for 5 years or longer. pERC heard from the clinical experts consulted by CDA-AMC that treatment options for third- or later-line settings for advanced RCC remain limited, with no established standard treatments for fourth-line advanced RCC. pERC agreed with the clinical experts that there is an unmet need for effective and safe therapy options in the requested patient population.
- **Efficacy outcomes:** The committee noted that, compared to treatment with everolimus, treatment with belzutifan resulted in statistically significant and clinically meaningful improvements in PFS and ORR associated with "high" to "moderate" levels of certainty per the CDA-AMC Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment. The committee discussed that OS results in the LITESPARK-005 trial showed that treatment with belzutifan likely results in little to no difference in the probability of being alive at 18 and 36 months compared to treatment with everolimus. The interpretation of OS was limited by imprecision in the estimates (wide CIs that crossed the null). In the absence of demonstrable OS gains, pERC discussed the clinical meaningfulness of PFS in the advanced RCC setting. pERC agreed with the clinical experts that the improvements in PFS of the magnitude observed in the LITESPARK-005 trial coupled with durable responses are of clinical importance in a heavily pretreated patient population that faces limited treatment options in later lines of therapy and with no standard therapies beyond the third line. For

the HRQoL outcome, the certainty of evidence was rated as low. pERC noted that despite the low certainty rating, treatment with belzutifan did not appear to have a detrimental effect on HRQoL, although analyses were descriptive and limited by missing data due to attrition.

- **Comparators:** pERC deliberated on the lack of evidence comparing belzutifan to relevant comparators in the Canadian clinical practice setting. According to the clinical experts, everolimus has largely been replaced by axitinib and cabozantinib and is rarely used in clinical practice. pERC discussed that the efficacy and safety of belzutifan compared to axitinib and cabozantinib remains unknown. pERC heard from clinical experts that, based on their experience, everolimus is expected to have efficacy and tolerability similar to axitinib in clinical practice. However, in the absence of comparative evidence between belzutifan and cabozantinib, the clinical experts anticipated that belzutifan will not replace cabozantinib except in cases in which cabozantinib is contraindicated or poorly tolerated. pERC heard from the clinical experts that belzutifan may be used after cabozantinib as a last-line therapy in third- or fourth-line treatment settings, where treatment options are limited.
- **Adverse events:** pERC deliberated on the safety profile of belzutifan. Evidence from the LITESPARK-005 trial suggested that the incidence of AEs of any grade, grade 3 to 5 AEs, and serious AEs (SAEs) was similar between the study groups. AEs in the belzutifan group were mostly driven by anemia, fatigue, and nausea. The percentage of patients with AEs resulting in treatment discontinuation was lower in the belzutifan group compared with the everolimus group. pERC discussed the risk of anemia and hypoxia with belzutifan treatment and noted that adequate monitoring and potential dose adjustments would be required. Overall, pERC agreed with the clinical experts that the safety profile of belzutifan appeared manageable.
- **Pricing:** The committee agreed that the total drug cost of treatment with axitinib, everolimus, or belzutifan should be comparable. pERC also noted that, if flat pricing of different strengths is in place, there is a potential for cost differences between these treatment options if alternative dosing schedules or dose reductions are used in practice.
- **Monitoring costs:** The Health Canada–approved product monograph states that health care providers should monitor oxygen saturation with pulse oximetry before initiation of treatment and regularly at follow-up visits throughout treatment with belzutifan. The product monograph states that some patients may experience asymptomatic hypoxia and that health care providers, at their discretion, may instruct patients to monitor oxygen saturation at home. The clinical experts consulted by CDA-AMC noted that, although not obligatory, home use of a pulse oximeter should be discussed with patients as a means of enhanced monitoring. pERC noted that other available treatments for the indication under review do not include recommendations in their respective product monographs regarding routine monitoring of oxygen saturation using pulse oximetry and that the sponsor did not include the costs associated with monitoring for hypoxia (including patient-specific oximeters) in the pharmacoeconomic analysis that was submitted to CDA-AMC. As such, the committee discussed that the economic implications of hypoxia monitoring and the feasibility of adoption for broader use of at-home monitoring have not been evaluated in the sponsor's application. The committee agreed that in cases in which at-home monitoring with a pulse oximetry is deemed a requirement by the treating

clinician, it is recommended that the costs associated with at-home monitoring be borne by the sponsor and not by the drug programs or broader health system.

- **Budget impact is uncertain**: If the use of belzutifan in clinical practice is reserved for patients in third- or fourth-line therapy, and no other subsequent therapy is available, belzutifan may take up the totality of the market shares and the 3-year budget impact could reach approximately $45.5 million.

Background

Kidney cancer is the eighth most common malignancy in Canada. In 2024, the incidence of kidney cancer in Canada was estimated at 9,000 people and the mortality rate was estimated as 3.9 per 100,000 people. RCC accounts for approximately 90% of all kidney cancers and is classified into various histologic subtypes. Approximately 25% of patients are diagnosed with locally advanced or metastatic RCC; 20% to 40% of patients with localized primary RCC will develop metastatic disease. Patients with RCC can experience a wide range of symptoms, although many show no symptoms until the disease is advanced. Flank pain, hematuria, and abdominal renal mass are symptoms that strongly suggest locally advanced RCC. Patients with RCC can also present with or subsequently develop systemic symptoms and paraneoplastic syndromes.

First-line treatment options for untreated advanced RCC are guided by the International Metastatic RCC Database Consortium (IMDC) risk group classification status. The standard first-line treatment for patients with advanced RCC in any IMDC risk category consists of an immuno-oncology (IO) agent in combination with a TKI or with TKI monotherapy. Among patients in the IMDC intermediate or poor risk categories, nivolumab plus ipilimumab is also a recommended first-line treatment option for advanced RCC. The strategy for subsequent lines of treatment is contingent on the treatments administered in the first-line setting for advanced RCC. Depending on the type of first-line treatment administered for RCC, later-line treatments for RCC may include TKI monotherapy, nivolumab, and everolimus. The clinical experts consulted by CDA-AMC stated that everolimus is less commonly used to treat advanced RCC due to the emergence of newer or more effective therapies (e.g., cabozantinib and axitinib) and it is currently not funded by most provinces after treatment with these monotherapies. There is an unmet need for effective later-line treatments for patients with advanced RCC, especially among those whose disease has progressed after treatment with an IO agent and a VEGF-TKI. Moreover, available treatment options for heavily pretreated RCC are often associated with side effects that are difficult to manage and negatively affect quality of life (QoL).

Belzutifan has been approved by Health Canada for the treatment of adult patients with advanced RCC following treatment with a PD-1 or PD-L1 inhibitor and a VEGF-TKI. Belzutifan is an antineoplastic drug. 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 1 phase III, open-label, active-controlled RCT in patients with advanced RCC after previous treatment with a PD-1 or PD-L1 inhibitor and a VEGF-TKI as well as 1 feasibility assessment for an indirect treatment comparison (ITC)
- patients' perspectives gathered by 1 patient group, Kidney Cancer Canada (KCC)
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with RCC
- input from 2 clinician groups, including the Ontario Health (OH) – Cancer Care Ontario (CCO) Genitourinary Cancers Drug Advisory Committee (GU DAC) with contribution from 2 clinicians as well as the Kidney Cancer Research Network of Canada (KCRNC) with contribution from 10 clinicians
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Group Input

An input was received from KCC for this submission. KCC is a national community of patients, caregivers, and health professionals who advocate and support patients with kidney cancer. KCC gathered the information through conducting an international online survey in affiliation with the International Kidney Cancer Coalition in 2022. The respondents consisted of 2,213 patients and caregivers from 39 countries, including 139 respondents (111 patients and 28 caregivers) from Canada. Furthermore, KCC conducted a survey in December 2024 and gathered information from 2 patients — 1 with kidney cancer and 1 with von Hippel-Lindau disease — and 1 caregiver of a patient with kidney cancer, all of whom had experience with belzutifan. The 2 patients also provided consent to have a telephone conversation. KCC noted that approximately one-quarter of patients reported that their current treatments were difficult to tolerate. The most commonly experienced barriers reported from respondents in Canada were wait times to treatment (16%), lack of access to local specialty doctors (10%), lack of access to up-to-date treatment or equipment (9%), cost of treatment (7%), and lack of personal support (5%). KCC explained that there is a general need for more effective therapies with manageable side effects, better predictive and prognostic biomarkers to guide treatment, and better early detection of disease. Based on the patient group input, unmet needs include treatments that are curative, durable remission, disease stability, long-term duration of response, improved tolerability, improved disease-specific QoL, and innovative medicines with new mechanisms. Additionally, according to the patient advocacy group, a new treatment needs to address the resistance to existing treatment because not all patients respond to currently available treatments and patients who do respond to currently funded treatments often become resistant to therapy after some time. All 3 respondents

with direct experience with belzutifan reported positive experiences with the drug, noting that the treatment was effective with tolerable side effects.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted by CDA-AMC agreed that there is an unmet need for the availability of third- and fourth-line treatments with novel mechanisms of action for advanced RCC. The importance of improving treatment options for heavily pretreated RCC was emphasized because disease progression occurs in almost all patients receiving treatment and available treatment options are associated with side effects that are difficult to manage and can negatively affect QoL.

The clinical experts stated that belzutifan would be administered in the third- or fourth-line treatment setting for patients with advanced RCC after prior treatment with a PD-1 or PD-L1 inhibitor and a VEGF-TKI. One expert agreed that belzutifan would cause a shift in the treatment paradigm for RCC due to the introduction of a new treatment option for third- and fourth-line settings and a novel mechanism of action. However, the magnitude of this shift remains unknown due to the small proportion of patients who are eligible for third- and fourth-line treatment for advanced RCC in Canada. The experts indicated that it was not possible to identify which subgroup of patients would receive more or less benefit from treatment with belzutifan.

One clinical expert indicated that the assessment of response to treatment for RCC consisted of CT scans performed every 3 months. One clinical expert stated that clinically meaningful responses for treatment for RCC included radiologic response, symptom status, stable disease, and adequate tolerance of the drug. The clinical experts agreed that discontinuation criteria for belzutifan consisted of disease progression and intolerable toxicities. Both experts also agreed that belzutifan should be prescribed by a medical oncologist experienced in managing advanced RCC. It was also noted that belzutifan can be administered at a patient's home. One expert noted that transfusions and dose reductions are preferred for the management of anemia and hypoxia related to belzutifan. Although the expert did not note variation in the management of AEs across jurisdictions in Canada, they noted that there may be variations in the coverage of home oxygen and erythropoietin, if required.

Clinician Group Input

CDA-AMC received 2 clinician inputs, 1 from the OH-CCO GU DAC with contribution from 2 clinicians and 1 from the KCRNC with contribution from 10 clinicians. The OH-CCO GU DAC provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program. The KCRNC is a virtual and inclusive national network of clinicians and researchers who treat kidney cancer in Canada. The KCRNC is a federally registered not-for-profit organization with commitment to enhance the knowledge of kidney cancer and its treatment.

Both clinician groups agreed that the first-line systemic treatment for advanced kidney cancer considers the IMDC risk groups. Based on the inputs, treatment goals included an improvement in OS and PFS with a reduction in the size of metastatic lesions (i.e., ORR), and an improved QoL by controlling symptoms

of disease. The clinician groups noted that the main gap is resistance to the currently available treatment modalities. The clinician groups agreed that belzutifan will be used in the later-line setting, either as a second-line treatment if the patient's disease progresses after a first-line combination regimen or as a third-line agent. Based on the clinician group inputs, radiological response and symptom improvement are used to determine treatment response.

Drug Program Input

The clinical experts consulted for this review 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	
The comparator in the phase III LITESPARK-005 trial was everolimus, which is no longer routinely used in Canada and not considered a relevant comparator. Jurisdictions follow the CDA-AMC provisional funding algorithm for metastatic RCC from a funding perspective, and patients are eligible for 1 immune checkpoint inhibitor and 2 TKI therapies. Depending on the choice of first-line therapy, there may be 2 or 3 lines of therapy that are funded. Potentially relevant comparators to belzutifan for the target patient population include cabozantinib and axitinib.	This is a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
Are patients with early relapses after adjuvant pembrolizumab (i.e., relapse within 6 months of completion) who later receive and progress on a TKI eligible for belzutifan?	Although a lack of data for these patients was noted, pERC agreed with the clinical experts that, due to limited treatment options, belzutifan should be available for patients with early relapses after adjuvant pembrolizumab (i.e., relapse within 6 months of completion) who later receive and progress on a TKI.
Most patients in LITESPARK-005 had clear cell RCC. Are other histological subtypes eligible for belzutifan? Note: Jurisdictions do not currently restrict metastatic RCC regimens by histology in the metastatic setting.	pERC agreed with the clinical experts consulted by CDA-AMC that histologic subtypes outside of clear cell RCC should not be eligible for belzutifan at this time. Belzutifan selectively targets a pathway (HIF-2 alpha) predominantly relevant to clear cell RCC. The clinical experts noted that FH-mutated RCC has increased HIF-1 alpha overexpression, which could potentially be targeted by belzutifan; however, there is insufficient evidence at this time to guide a recommendation on this.
Should all IMDC risk categories be eligible? Are all IMDC risk categories expected to benefit similarly?	pERC agreed with the clinical experts consulted by CDA-AMC that patients within all IMDC risk categories should be eligible for belzutifan. The LITESPAERK-005 trial enrolled patients across favourable (21.7%), intermediate (66.1%), and poor risk (12.2%) categories.

Implementation issues	Response
Considerations for discontinuation of therapy	
What are the discontinuation criteria for belzutifan?	pERC agreed with the clinical experts consulted by CDA-AMC that disease progression and unmanageable toxicity are key factors in deciding to discontinue treatment with belzutifan. In line with the protocol criteria of the LITESPARK-005 trial, pERC agreed with the clinical experts that treatment with belzutifan could be continued beyond disease progression until clinically meaningful progression occurs based on the judgment of the treating clinician.
Considerations for prescribing of therapy	
The recommended dose of belzutifan is 120 mg (three 40 mg tablets) administered orally once daily, with or without food.	This is a comment from the drug programs to inform pERC deliberations.
Generalizability	
Should patients who have received treatment PD-1 or PD-L1 inhibitors and VEGF-TKIs who are on second- or third-line therapies be switched to belzutifan or should belzutifan be used as the next line of therapy?	pERC agreed with the clinical experts consulted by CDA-AMC that belzutifan should be reserved for the next line of therapy, citing that there is currently a lack of data to suggest that belzutifan performs substantially better than key comparators (e.g., cabozantinib and axitinib).
Funding algorithm	
Request an initiation of a rapid provisional funding algorithm. Drug may change place in therapy of drugs reimbursed in subsequent lines.	This is a comment from the drug programs 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.	This is a comment from the drug programs to inform pERC deliberations.
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. • Exposure to belzutifan during pregnancy can cause embryofetal harm. • Verify pregnancy status before the initiation of belzutifan. • Advise patients of these risks and the need for effective nonhormonal contraception. • Belzutifan can render some hormonal contraceptives ineffective.	This is a comment from the drug programs to inform pERC deliberations.
System and economic issues	
Confidential pCPA pricing exists for nivolumab, pembrolizumab, and many of the TKIs and generic everolimus.	This is a comment from the drug programs to inform pERC deliberations.
Drug programs are concerned about the potential large budget impact given the volume of patients with metastatic RCC. Under what clinical circumstances would	The clinical experts consulted by CDA-AMC noted that exact clinical circumstances have not yet been defined. The clinical experts anticipated that belzutifan would be offered when

Implementation issues	Response
belzutifan be preferred over other funded options if there is a choice?	other treatment options have been exhausted. pERC agreed with the clinical experts that belzutifan provides access to an additional line of therapy for RCC and that a minority of patients, approximately 20% and 7% of patients, respectively, go on to receive third- and fourth-line treatment.

CDA-AMC = Canada's Drug Agency; FH = fumarate hydratase; HIF = hypoxia inducible factor; IMDC = International Metastatic RCC Database Consortium; pCPA = Pan-Canadian Pharmaceutical Alliance; PD-1 = programmed death receptor-1; PD-L1 = programmed death-ligand 1; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

Clinical Evidence

Systematic Review

Description of Studies

One pivotal phase III, open-label, active-controlled RCT (LITESPARK-005) evaluated the efficacy and safety of belzutifan (n = 374) compared to everolimus (n = 372) in patients with advanced RCC who were previously treated with a PD-1 or PD-L1 inhibitor and a VEGF-TKI. The trial enrolled adult patients with unresectable, locally advanced, or metastatic clear RCC and who were required to have had disease progression on or after having received treatment with both a PD-1 or PD-L1 inhibitor and VEGF-TKI.

Patients were required to have adequate organ function, a Karnofsky Performance Score (KPS) of at least 70, and have received no more than 3 prior systemic regimens for locally advanced or metastatic RCC. Randomization of patients in the trial was stratified according to IMDC prognostic score (0 versus 1 to 2 versus 3 to 6) and the number of prior VEGF and VEGF receptor–targeted therapies for advanced RCC (1 versus 2 to 3). The primary outcomes of the LITESPARK-005 trial were PFS based on blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and OS. The secondary outcomes of the trial were ORR based on BICR per RECIST 1.1, duration of response (DOR), HRQoL, and safety. The baseline demographic and disease characteristics were balanced between treatment groups. The median age of patients in the trial was 63 years (range, 22 to 90 years) and most patients were male (77.9%; female = 22.1%).

Patients in the trial were of the following races and ethnicities (categories from original source): American Indian or Alaska Native (0.7%), Asian (12.1%), Black or African American (1.1%), multiple (2.3%), Native Hawaiian or other Pacific Islander (0.1%), white (78.8%); 5.0% of patients had missing data for race and ethnicity. Most patients had a KPS ranging between 90 and 100 (64.1%) and most patients had an Eastern Cooperative Oncology Group (ECOG) score of 1 (55.1%). Most patients had an intermediate or poor IMDC prognostic risk score (78.3%) and most had stage IV RCC at diagnosis (57.0%). Most patients had 2 or more organs involved with disease at baseline (91.2%), with the lung being the most common site of metastatic disease (64.6%). Most patients had a prior nephrectomy (69.7%), received 2 (43.3%) or 3 (42.8%) prior lines of therapy, and received 1 prior VEGF- or VEGF receptor–targeted therapy (50.5%).

Efficacy Results

Progression-Free Survival Based on BICR per RECIST 1.1

At the time of the first interim analysis (data cut-off: November 1, 2022), the median duration of follow-up was 13.6 months (range, 0.2 to 31.1 months) for the belzutifan group and 13.3 months (range, 0.8 to 31.8 months) for the everolimus group. At the time of data cut-off for this analysis, 519 PFS events (82.9% of 626 total expected events at the final analysis) had occurred (257 patients in the belzutifan group and 262 patients in the everolimus group). The corresponding HR was 0.75 (95% CI, 0.63 to 0.90; 1-sided P = 0.00077), representing a 25% reduction in the risk of disease progression or death with belzutifan compared with everolimus. The predefined success criterion for superiority based on PFS was met at the first interim analysis. The median PFS was similar for both the belzutifan and everolimus groups (5.6 months [95% CI, 3.9 to 7.0 months] for the belzutifan group compared with 5.6 months [95% CI, 4.8 to 5.8 months] for the everolimus group). In addition, PFS rates based on Kaplan-Meier (KM) estimates were higher in the belzutifan group compared with the everolimus group at all specified time points. The estimated PFS rate at 24 months was [redacted] for the belzutifan group compared with 0% (95% CI, not applicable) for the everolimus group (between-group difference for belzutifan compared with everolimus = [redacted]). The PFS results across additional sensitivity analyses were consistent with those of the overall intention-to-treat (ITT) population and results across all prespecified subgroups favoured belzutifan over everolimus.

At the time of the final analysis (data cut-off: April 15, 2024), the median duration of follow-up was 21.4 months (range, 0.2 to 47.6 months) for the belzutifan group and 18.3 months (range, 0.8 to 49.2 months) for the everolimus group. At the time of data cut-off for this analysis, 587 PFS events had occurred (308 patients in the belzutifan group and 279 patients in the everolimus group). The HR for PFS was 0.75 (95% CI, 0.63 to 0.88; 1-sided P = 0.00034). Similar to what was observed for the first interim analysis, the median PFS measured at the final analysis remained similar for the belzutifan and everolimus groups. Moreover, PFS rates based on KM estimates continued to be higher in the belzutifan group compared with the everolimus group at all specified time points. The estimated PFS rate at 30 months was 14.2% (95% CI, 10.7% to 18.2%) for the belzutifan group compared with 2.7% (95% CI, 1.1% to 5.5%) for the everolimus group (between-group difference for belzutifan compared with everolimus = 11.5%; 95% CI, 7.2% to 15.8%).

Overall Survival

The OS end point was not statistically significant at any of the prespecified analyses (interim and final analyses) of the trial. At the time of the final analysis (data cut-off: April 15, 2024), the median duration of follow-up was 21.4 months (range, 0.2 to 47.6 months) for the belzutifan group and 18.3 months (range, 0.8 to 49.2 months) for the everolimus group. There were 513 observed OS events (approximately 106% of the 483 events planned for the final analysis; 254 occurring in the belzutifan group and 259 occurring the everolimus group). The corresponding HR was 0.92 (95% CI, 0.77 to 1.10; 1-sided P = 0.17644), which was not statistically significant. The median OS was 21.4 months (95% CI, 18.2 to 24.3 months) in the belzutifan group compared with 18.2 months (95% CI, 15.8 to 21.8 months) in the everolimus group. The OS rates based on KM estimation were numerically higher in the belzutifan group compared with the everolimus group at all specified time points. The estimated OS rate at 36 months was [redacted]

[redacted] for the belzutifan group compared with 28.0% (95% CI, 23.1% to 33.1%) for the everolimus group (between-group difference for belzutifan compared with everolimus = [redacted]. The OS results across all prespecified subgroups were consistent with those of the overall ITT population.

Objective Response Rate Based on BICR per RECIST 1.1

At the time of the first interim analysis (data cut-off: November 1, 2022), the ORR based on BICR per RECIST v1.1 for the belzutifan group was [redacted] compared to 3.5% (99.9% CI, 1.2% to 7.8%). The estimated difference in the percentage of patients with confirmed ORR for belzutifan versus everolimus was [redacted]. The P value crossed the prespecified boundary for statistical significance of 0.001 at the time of the first interim analysis. A higher proportion of patients had confirmed complete response (CR) and partial response (PR) in the belzutifan group (CR = 2.7%; PR = 19.3%) than in the everolimus group (CR = 0%; PR = 3.5%). At the time of the second interim analysis (data cut-off: June 13, 2023), the ORR was 22.7% (99.9% CI, 16.1% to 30.5%) for the belzutifan group compared to 3.5% (99.9% CI, 1.2% to 7.8%) for the everolimus group. The estimated difference in the percentage of patients with confirmed ORR for belzutifan versus everolimus was 19.2% (99.9% CI, 11.8% to 27.5%; 1-sided nominal P < 0.00001). At the time of the final analysis (data cut-off: April 15, 2024), results of ORR for belzutifan compared to everolimus remained consistent with those of the second interim analysis.

Duration of Response

At the time of the first interim analysis (data cut-off date: November 1, 2022), the median DOR based on BICR per RECIST 1.1 was not yet reached (range, 1.7[ongoing] to 23.2 [ongoing] months) for the belzutifan group and was 17.2 months (range, 3.8 to 18.0 [ongoing] months) for the everolimus group. The proportion of those with a response was higher in the belzutifan group than the everolimus group at each response duration time point (i.e., 6 months through 21 months) based on KM estimates; 74.2% of patients with a response in the belzutifan group and 68.4% in the everolimus group had a DOR lasting 12 months or longer.

At the time of the final analysis (data cut-off date: April 15, 2024), the median DOR was 19.3 months (range, 1.9 [ongoing] to 40.1 [ongoing] months) in the belzutifan group and 13.7 months (range, 3.8 to 29.5 [ongoing] months) in the everolimus group. Similar to what was observed during the first interim analysis, the proportion of those with a response was higher in the belzutifan group compared with the everolimus group at all measured time points based on KM estimates during the second interim and final analysis.

Time to Response

At the time of the first interim analysis (data cut-off date: November 1, 2022), the median time to response was 3.7 months (range, 1.7 to 16.6 months) for the belzutifan group and 3.7 months (range, 1.8 to 5.4 months) for the everolimus group. At the time of the final analysis (data cut-off date: April 15, 2024), the median time to response was 3.8 months (range, 1.7 to 22.0 months) for the belzutifan group and 3.7 months (range, 1.8 to 5.7 months) for the everolimus group.

Health-Related Quality of Life

The key HRQoL outcomes of interest identified from the LITESPARK-005 trial were the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS) scores, which were measured at the first and second interim analyses. Results for HRQoL outcomes of interest were not assessed at the final analysis. These outcomes were not controlled for multiplicity; thus, all reported P values and CIs are nominal and descriptive. At the time of the first analysis (data cut-off date: November 1, 2022), the belzutifan group had no change in EORTC QLQ-C30 global health status (GHS)/QoL scores from baseline to week 17 (least squares [LS] = [redacted], whereas patients in the everolimus group reported a numerical decrease (worsening) in score from baseline (LS mean = −6.13; 95% CI, −8.51 to −3.75). The difference in LS mean change in EORTC QLQ-C30 GHS/QoL score from baseline to week 17 between the 2 groups was [redacted]. Both groups reported a numerical decrease (worsening) in FKSI-DRS score from baseline to week 17, with a larger decrease in score noted for patients in the everolimus group (LS mean change = 1.61 points; 95% CI, −2.17 to −1.06 points) compared with the belzutifan group (LS mean change = −0.07 points; 95% CI, −0.59 to 0.45 points). The difference in LS mean change in FKSI-DRS score from baseline between the belzutifan and everolimus groups was 1.54 points (95% CI, 0.81 to 2.28 points; nominal P < 0.0001). Moreover, the time to deterioration in HRQoL was longer for belzutifan over everolimus in terms of the EORTC QLQ-C30 GHS/QoL and FKSI-DRS scores. The results for the second interim analysis (data cut-off date: June 13, 2023) were consistent with those reported at the first interim analysis.

Harms Results

At the time of the final analysis (data cut-off date: April 15, 2024), almost all patients in the LITESPARK-005 trial reported at least 1 AE (99.2% for both belzutifan and everolimus treatment groups). The most common AE in both treatment groups was anemia (83.1% in the belzutifan group compared with 57.2% in the everolimus group) followed by fatigue (32.3%) and nausea (18.5%) in the belzutifan group and stomatitis (38.1%) and fatigue (25.8%) in the everolimus arm. At least 1 SAE was reported in [redacted] of patients in the belzutifan group and 38.6% of patients in the everolimus group, with the most common SAEs reported being hypoxia (7.3% in the belzutifan group and none in the everolimus group) and anemia (5.4% in the belzutifan group and 2.2% in everolimus group). Higher rates of discontinuation of study treatment due to AEs were noted among patients in the everolimus group (15.3%) than those in the belzutifan group [redacted]. The most common AEs that led to treatment discontinuation in both treatment groups were related to respiratory, thoracic, and mediastinal disorders (1.9% for the belzutifan group compared with 6.4% for the everolimus group). Death due to AEs was slightly higher among patients in the everolimus group (5.3%) than patients in the belzutifan group (3.8%). The most common AEs that led to death in both groups were related to infections and infestations (0.8% in the belzutifan group versus 3.1% for the everolimus group).

Anemia, hypoxia, and dyspnea were identified as clinical AEs of interest because they have been noted to be associated with treatment with belzutifan. At the final analysis, a higher rate of anemia was reported in patients in the belzutifan group compared with patients in the everolimus group (83.3% for the belzutifan

group compared with 57.5% for the everolimus group). Of the events related to anemia, most were grade 2 in both groups(41.9% for the belzutifan group compared with 29.7% for the everolimus group). Moreover, a higher rate of hypoxia was reported in the belzutifan group compared with patients in the everolimus group (14.2% for the belzutifan group compared with 1.1% for the everolimus group). Of the events related to hypoxia, most events related to hypoxia were grade 3 in both groups (10.5% for the belzutifan group versus 0.8% for the everolimus group). Similar rates of dyspnea were reported in patients receiving belzutifan (15.3%) and everolimus (14.4%). For all 3 clinical AEs of interest, the rates of discontinuation among both treatment groups were low.

Critical Appraisal

Notable strengths of the trial included the use of an ITT analysis and the stratification of randomization according to IMDC prognostic scores and the number of prior VEGF-targeted therapies for advanced RCC. The randomization process of the trial was deemed appropriate, although there was limited detail provided on how randomization numbers allocated to patients were obtained. Moreover, the LITESPARK-005 trial had an open-label study design which indicated that patients and investigators were not blinded to treatment. Although PFS and ORR were assessed based on BICR, the lack of blinding of patients may have contributed to performance bias in results for patient-reported outcomes. The 2 treatment groups were balanced in terms of baseline patient and disease characteristics. Prior and concomitant non-oncologic medications were overall balanced between the 2 treatment groups. Some imbalances in categories of concomitant medications were deemed to have minimal impact on treatment effect by the clinical experts consulted by CDA-AMC.

It was also noted that more patients in the everolimus group received subsequent oncologic therapies compared with patients in the belzutifan group. This difference could potentially introduce a confounding effect on OS because the survival results might be partially attributable to treatments administered after disease progression rather than the study treatment itself. This difference could favour the everolimus group; however, the risk of bias due to deviations from the intended interventions was deemed to be low by the clinical experts consulted by CDA-AMC. The clinical experts consulted by CDA-AMC also confirmed that the oncologic therapies used in the LITESPARK-005 trial were largely reflective of those used in Canadian clinical practice, although some differences in treatment sequence were observed. For instance, 19.0% of patients in the LITESPARK-005 trial received cabozantinib as a subsequent therapy after belzutifan or everolimus, whereas the clinical experts consulted by CDA-AMC anticipated that cabozantinib would be used first, followed by belzutifan. The clinical experts noted, if belzutifan were publicly reimbursed, most patients in clinical practice would be expected to receive belzutifan as third-line treatment or, to a lesser extent, fourth-line treatment, whereas cabozantinib would mainly remain as a second-line treatment. After treatment with belzutifan, the clinical experts anticipated there would be no further approved treatment options in clinical practice in Canada.

In the LITESPARK-005 trial, approximately 13%, 43%, 43%, and 1% of patients received 1, 2, 3, or 4 prior lines of therapy, with the majority receiving third- or fourth-line treatment. Exploratory subgroup results for OS and PFS by line of therapy (i.e., 1, 2, or 3 prior lines of therapy) were consistent with those for the overall

trial population. Although some uncertainty remains regarding the impact of differences in prior lines of therapy between the trial and expected clinical practice on the generalizability of results, the clinical experts consulted by CDA-AMC felt it would be reasonable to generalize the trial results to anticipated clinical practice and did not raise concerns regarding the applicability of the LITESPARK-005 trial results in the Canadian clinical context.

Visual inspection of the KM curves by the CDA-AMC review team revealed that the PFS curves for the intervention and comparator treatment arms crossed multiple times and did not separate until approximately 6 months. Although this suggests that the HRs, which were based on proportional hazard models, may not accurately reflect the treatment effect over time, it is likely a result of variation in effects between the treatment and an active control during the early stages of treatment initiation. The clinical experts consulted by CDA-AMC suggested that belzutifan may have a longer duration of efficacy compared to everolimus, which may explain why the benefit of belzutifan is observed at later time points beyond those corresponding to the median PFS. The KM-estimated between-group differences in the probability of PFS at clinically relevant follow-up times were not affected by this limitation.

The primary analysis for PFS and ORR was assessed at the first interim analysis, which may potentially result in overestimation of treatment effect for belzutifan. However, 519 PFS events had occurred at the first interim analysis, which constituted 82.9% of the total expected events for PFS at the final analysis. Moreover, the results for PFS and ORR at the first interim analysis were overall consistent with those measured at the final analysis. Thus, the review team determined that the risk of overestimation was small. For the assessment of PFS by BICR per RECIST 1.1, a larger proportion of patients in the everolimus group (18.3%) were censored due to the initiation of new anticancer therapy before a PFS event than those in the belzutifan group (5.6%). However, the trial performed sensitivity analyses that counted the initiation of new anticancer therapy as a PFS event. The results of these analyses were consistent with those of the primary analysis for the ITT population, which suggested that the between-group imbalances in patients starting new anticancer therapy had little impact on the results for PFS.

Key HRQoL outcomes from the LITESPARK-005 trial were measured using the EORTC QLQ-C30 and FKSI-DRS instruments. The interpretation of results for HRQoL is limited by the lack of adjustments for multiple testing, low completion rates at later time points, and imbalances in missing data between the 2 groups.

The LITESPARK-005 trial assessed the safety and efficacy of belzutifan compared with everolimus. Although once considered a standard treatment for pretreated advanced RCC, the clinical experts consulted by CDA-AMC agreed that everolimus is a less relevant comparator for later-line advanced RCC compared to axitinib or cabozantinib and is rarely used in Canadian clinical practice. Thus, the stand-alone results of the trial may not provide a full assessment of the efficacy and safety of belzutifan compared to existing treatments for advanced RCC in Canadian clinical practice. The clinical experts consulted by CDA-AMC suggested that everolimus may be similar to axitinib in terms of efficacy based on how these drugs perform in clinical practice. Aside from AEs related to the mechanism of action of belzutifan (i.e., anemia and hypoxia), the clinical experts did not suggest additional safety concerns of belzutifan compared to other key comparators for RCC in Canada. Of note, pERC previously discussed that everolimus was similar to axitinib in terms of

efficacy and safety as a part of the recommendation for funding cabozantinib for the treatment of advanced RCC. The clinical experts noted there is currently a lack of head-to-head RCTs and no evidence to suggest that belzutifan performs substantially better than cabozantinib. According to the clinical experts consulted by CDA-AMC, treatment options for third- or later-line settings for advanced RCC remain limited, with a lack of standard treatment options noted for fourth-line advanced RCC. The experts emphasized that a treatment's ability to delay progression and achieve response in these treatment settings would be highly valued in clinical practice.

Based on sponsor-submitted studies assessing PFS as a surrogate for OS, it remains unclear whether PFS could be interpreted as a surrogate outcome for OS for the target population of this review.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessments for PFS, OS, ORR, SAEs, and discontinuation due to AEs were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review. The reference point for the certain of evidence assessment for the EORTC QLQ-C30 GHS/QoL score was sourced from the literature.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: clinical outcomes (PFS, OS, ORR), HRQoL (EORTC QLQ-C30 GHS/QoL), and harms (SAEs, discontinuation due to AEs). Table 3 presents the GRADE summary of findings for belzutifan versus everolimus.

Table 3: Summary of Findings for Belzutifan vs. Everolimus for Patients With Advanced RCC

Outcome and follow-up	Patients, N (studies)	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Everolimus	Belzutifan	Difference		
Progression-free survival in the ITT population, interim analysis 1 (data cut-off: November 1, 2022)							
Probability of being alive and progression-free at 12 months Follow-up (median): Belzutifan: 13.6 months Everolimus: 13.3 months	746 (1 RCT)	NR	171 per 1,000 patients	[redacted]	[redacted]	High[a,b]	Belzutifan results in a clinically important increase in the probability of patients being alive and progression-free at 12 months compared with everolimus.
Probability of being alive and progression-free at 18 months Follow-up (median): Belzutifan: 13.6 months Everolimus: 13.3 months	746 (1 RCT)	NR	83 per 1,000 patients	[redacted]	[redacted]	High[a,b]	Belzutifan results in a clinically important increase in the probability of patients being alive and progression-free at 18 months compared with everolimus.
Probability of being alive and progression-free at 24 months Follow-up (median): Belzutifan: 13.6 months Everolimus: 13.3 months	746 (1 RCT)	NR	0 per 1,000 patients	[redacted]	[redacted]	Moderate[a,c]	Belzutifan likely results in a clinically important increase in the probability of patients being alive and progression-free at 24 months compared with everolimus.
Overall survival in the ITT population, final analysis (data cut-off: April 15, 2024)							
Probability of being alive at 18 months Follow-up (median): Belzutifan: 21.4 months Everolimus: 18.3 months	746 (1 RCT)	NR	507 per 1,000 patients	[redacted]	[redacted]	Moderate[d]	Belzutifan likely results in little to no difference in the probability of patients being alive at 18 months compared with everolimus.

Outcome and follow-up	Patients, N (studies)	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Everolimus	Belzutifan	Difference		
Probability of being alive at 36 months Follow-up (median): Belzutifan: 21.4 months Everolimus: 18.3 months	746 (1 RCT)	NR	280 per 1,000 patients	[redacted]	[redacted]	Moderate[d]	Belzutifan likely results in little to no clinically important difference in the probability of patients being alive 36 months compared with everolimus.
Objective response rate in the ITT population, interim analysis 1 (data cut-off: November 1, 2022)							
Proportion of patients with CR or PR[e] Follow-up (median): Belzutifan: 13.6 months Everolimus: 13.3 months	746 (1 RCT)	NR	35 per 1,000 patients	[redacted]	[redacted]	High[a,f]	Belzutifan results in a clinically important increase in objective response rate compared with everolimus.
Health-related quality of life in the PRO FAS population, interim analysis 1 (data cut-off: November 1, 2022)							
LS mean change from baseline in EORTC QLQ-C30 (GHS/QoL scale) at week 17 Follow-up (median): Belzutifan: 13.6 months Everolimus: 13.3 months	724 (1 RCT)	NR	−6.13	[redacted]	[redacted]	Low[a,g,h]	Belzutifan may result in little to no clinically important difference in LS mean change from baseline in EORTC QLQ-C30 (GHS/QoL) at week 17 compared with everolimus.
Harms in the APaT population, final analysis (data cut-off: April 15, 2024)							
Proportion of patients with SAEs Follow-up (median): Belzutifan: 21.4 months Everolimus: 18.3 months	732 (1 RCT)	NR	386 per 1,000 patients	[redacted]	[redacted]	Moderate[g,i]	Belzutifan likely results in little to no difference in the proportion of patients with ≥ 1 SAEs compared with everolimus.
Proportion of patients with AEs leading to discontinuation Follow-up (median):	732 (1 RCT)	NR	153 per 1,000 patients	[redacted]	[redacted]	Moderate[g,j]	Belzutifan likely results in a clinically important decrease in the proportion of patients

Outcome and follow-up	Patients, N (studies)	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Everolimus	Belzutifan	Difference		
Belzutifan: 21.4 months Everolimus: 18.3 months					[redacted]		with ≥ 1 AEs leading to discontinuation compared with everolimus.

AE = adverse event; APaT = all patients as treated; CI = confidence interval; CR = complete response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FAS = full analysis set; GHS = global health status; ITT = intention to treat; LS = least squares; NR = not reported; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; QoL = quality of life; RCC = renal cell carcinoma; RCT = randomized controlled trial; SAE = serious adverse event.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Values for the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment of this outcome were sourced from an interim analysis. Although limitations regarding internal validity were identified regarding results from interim analyses, certainty was not rated down for risk of bias because this limitation was determined to have a small or no impact on the results.

[b]Was not rated down for imprecision. There is no established between-group minimal important difference (MID) for PFS rate at 12 or 18 months, but the clinical experts consulted by Canada's Drug Agency (CDA-AMC) considered that a 10% difference between groups in the probability of patients who were alive and progression-free at this time point could be considered a threshold of clinical importance. The point estimate for the between-group difference suggested a clinically important difference between the 2 groups and the CDA-AMC review team determined that the lower bound of the 95% CI did not appreciably cross the 10% threshold.

[c]Rated down 1 level for serious imprecision. There is no established between-group MID for PFS rate at 24 months, but the clinical experts consulted by CDA-AMC considered that a 10% difference between groups in the probability of patients who were alive and progression-free at this time point could be considered a threshold of clinical importance. A 95% CI could not be calculated for the between-group difference in the probability of patients who were alive and progression-free at 24 months. This was because the 95% CI corresponding to the PFS rate of the everolimus group was not evaluable at 24 months because no patients in the everolimus group survived to this time point.

[d]Rated down 1 level for serious imprecision. There is no established between-group MID for overall survival rate at 18 or 36 months, but the clinical experts consulted by CDA-AMC considered that a 5% difference between groups in the probability of patients who were alive at this time point could be considered a threshold of clinical importance. The point estimate and lower bound of the 95% CI for the between-group difference suggested no clinically important difference between the 2 groups while the upper bound of the 95% CI suggested a clinically important difference for belzutifan vs. everolimus based on a 5% threshold.

[e]Based on the procedure for testing for multiplicity in the trial, the ultimate alpha used for testing objective response rate (ORR) was determined to be 0.001. Thus, 99.9% CIs were used for the GRADE assessment of ORR.

[f]Not rated down for imprecision based on a threshold of 10%. There is no established between-group MID for ORR, but the clinical experts consulted by CDA-AMC considered that a 10% difference between groups in the proportion of patients who achieved ORR could be considered a threshold of clinical importance. The point estimate and both upper and lower bounds of the 95% CI for the between-group difference suggested a clinically important difference between the belzutifan and everolimus groups based on a 10% threshold.

[g]The statistical testing for this end point was not adjusted for multiplicity in the LITESPARK-005 trial and should be considered as supportive evidence.

[h]Not rated down for imprecision. Although no literature was identified that estimated MIDs specifically in patients with advanced RCC, a change of 10 points in the EORTC QLQ-C30 scale score and summary score is conventionally considered to be a MID.[30] The point estimate and both upper and lower bounds of the 95% CI for the between-group difference did not suggest a clinically important difference between the belzutifan and everolimus groups based on a 10 point threshold. Rated down 2 levels for risk of bias due to reporting of outcome being affected by open-label study design and low completion rates of the assessment at week 17.

[i]Rated down 1 level for serious imprecision. There is no established between-group MID for the proportion of patients with SAEs, but the clinical experts consulted by CDA-AMC considered that a 10% difference between groups in the proportion of patients with SAEs could be considered a threshold of clinical importance. The point estimate and lower bound of the 95% CI for the between-group difference suggested little to no difference between the 2 groups while the upper bound of the 95% CI suggested important harm for belzutifan vs. everolimus based on a 10% threshold.

[j]Rated down 1 level for serious imprecision. There is no established between-group MID for the proportion of patients with AEs leading to discontinuation, but the clinical experts consulted by CDA-AMC considered that a 5% difference between groups in the proportion of patients with AEs leading to discontinuation could be considered a threshold of clinical importance. Although the 95% CI did not appreciably cross the 5% threshold for a clinically important effect, the effect estimate is based on few events.

Indirect Comparisons

In the absence of direct evidence comparing belzutifan to cabozantinib for the treatment of advanced RCC, the sponsor conducted a feasibility assessment for ITCs comparing belzutifan and cabozantinib in patients with advanced RCC after prior treatment with an immune checkpoint inhibitor and an antiangiogenic therapy. The assessment was conducted using data from the pivotal trials, LITESPARK-005 (belzutifan) and METEOR (cabozantinib). The METEOR trial had subgroup data available for patients who had received prior treatment with an IO agent and VEGF-TKI.

Both trials were phase III, open-label RCTs that evaluated patients with advanced clear cell RCC, a minimum KPS of 70, and had everolimus as a common comparator to their respective interventions. However, the trials significantly differed in terms of ECOG score and prior therapy. Heterogeneity between the trials in terms of ECOG performance status, prior lines of therapy, and type of prior therapy would have the potential to introduce bias into indirect comparisons if differences in these factors were not accounted for. Moreover, the subgroup of patients from the METEOR trial was noted to have a small sample size (n = 32 patients) and was expected to introduce significant uncertainty in the analyses.

To minimize bias from heterogeneity in patient baseline characteristics, the feasibility of conducting alternative methods of ITCs was also assessed, which included unadjusted (i.e., Bucher method) or adjusted (i.e., matching-adjusted indirect comparison [MAIC]) approaches. The Bucher method was deemed to be infeasible due to compromised randomization in the METEOR trial's subgroup of patients previously treated with IO agents and a VEGF-TKI, whereas MAICs were infeasible due to lack of reporting of key effect modifiers (i.e., IMDC risk classification and number of prior lines of therapy) for this subgroup. The small sample size of the subgroup was also a key limitation for both approaches due to its potential to introduce uncertainty in the analysis. Based on the results of the feasibility assessment, the CDA-AMC review team agreed that neither network meta-analyses (i.e., Bucher ITC) nor alternative methods of MAICs (i.e., anchored MAICs) were likely to provide unbiased treatment effect estimates for the comparison of belzutifan and cabozantinib for the treatment of adult patients with RCC.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with advanced RCC that has progressed after prior PD-1 or PD-L1 inhibitor and VEGF-targeted therapies
Treatment	Belzutifan
Dose regimen	120 mg once daily until disease progression or unacceptable toxicity occurs

Component	Description
Submitted price	Belzutifan: $213.33 per 40 mg tablet
Submitted treatment cost	The 28-day cost of belzutifan was $16,551 as calculated by the sponsor (accounting for dose reductions and dose skipping).
Comparators	• Everolimus • Axitinib
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (38 years)
Key data sources	• LITESPARK-005 trial comparing belzutifan with everolimus • Assumption that axitinib has comparable efficacy and safety to everolimus
Key limitations	• The use of a piece-wise approach to the extrapolation of PFS does not adequately capture the uncertainty surrounding PFS for the first 27 weeks as it is based directly on Kaplan-Meier data (i.e., no variability) and extrapolated over 38 years based on parametric distribution fitted to the post–27-week data. • The sponsor's base-case analysis predicts a survival benefit with belzutifan compared to everolimus (incremental LYs = 0.53) over a 38-year time horizon; however, no clinically relevant difference in survival was observed in the LITESPARK-005 trial (median follow-up = 35.8 months). Evidence submitted by the sponsor was deemed insufficient to establish the relationship between PFS and OS; therefore, it remains unclear whether PFS could be interpreted as a surrogate outcome for OS in the modelled population. Although axitinib is the most relevant comparator in clinical practice, comparisons of belzutifan with axitinib were based entirely on an assumption of equal efficacy between axitinib and everolimus. Therefore, the predicted OS benefit with belzutifan based on the sponsor's model is highly uncertain. • In the sponsor's model, the treatment effect of belzutifan persists indefinitely because no treatment waning was assumed, which can overestimate the benefit in the extrapolated period. Clinical experts indicated it is plausible for the effect of belzutifan to wane and noted the lack of evidence for long-term effectiveness. • Patients' prior and subsequent exposure to therapies in the model were not aligned with clinical practice in Canada. After treatment with belzutifan, the clinical experts anticipate there would be no further approved treatment options in clinical practice in Canada. The use of belzutifan is expected to be in third- or fourth-line therapy following cabozantinib, which was not reflected in the sponsor's parameterization of subsequent treatment. Notably, the most relevant comparator for belzutifan in third and fourth line would be axitinib, for which there is no comparative efficacy data available.
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by making changes to the following model parameters: adopting one-piece extrapolation of PFS and assuming treatment waning begins at 35.8 months and ends at 72 months (at which all comparators have the same effect). • CDA-AMC could not address the remaining limitations surrounding uncertainty in the OS benefit, lack of data informing belzutifan vs. axitinib, and concerns with the generalizability of the trial results given the trial population's prior exposure to therapies and subsequent treatments received. • In the CDA-AMC base case, belzutifan was associated with an ICER of $731,313 per QALY gained compared to everolimus (incremental costs = $214,542; incremental QALYs = 0.29). While still assuming axitinib with the same efficacy as everolimus, belzutifan was associated with an ICER of $664,048 per QALY gained compared to axitinib (incremental costs = $194,792; incremental QALYs = 0.29). To be considered cost-effective at a WTP threshold of $50,000 per QALY gained, belzutifan would require price reductions of 82% relative to everolimus and 74% relative to axitinib.

Component	Description
Key scenario analysis	• CDA-AMC conducted scenario analyses to evaluate the impact of excluding subsequent treatment from the analysis in which the ICER increased slightly to $751,204 per QALY gained vs. everolimus and $683,740 per QALY gained vs. axitinib.

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PD-1 = programmed death receptor-1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; QALY = quality-adjusted life-year; RCC = renal cell carcinoma; VEGF-TKI = vascular endothelial growth factor tyrosine kinase inhibitor; WTP = willingness to pay.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the market shares of comparators are uncertain and seem to overestimate the current use of everolimus in Canadian clinical practice, the number of eligible patients is uncertain because certain inputs to derive this number were based on clinical expert opinion, and the assumed distribution of subsequent therapy use lacks generalizability and is not aligned with current Canadian clinical practice.

Based on the CDA-AMC base case, the estimated budget impact of funding belzutifan for the treatment of adult patients with advanced RCC following a PD-1 or PD-L1 inhibitor and a VEGF-TKI was $629,470 in year 1, $3,752,798 in year 2, and $8,253,600 in year 3, for a 3-year total of $12,635,867. However, these estimates are uncertain because they still include patients in second-line and subsequent therapies.

CDA-AMC conducted scenario analyses to address remaining uncertainty. Assuming no subsequent treatment, the estimated 3-year budget impact of belzutifan increased to $13,177,556. When assuming that belzutifan is only used in third- and fourth-line treatment and it completely displaces everolimus and axitinib, as expected by the clinical experts, the estimated 3-year budget impact of belzutifan increased to $45,541,370.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice-Chair), Dr. Phillip Blanchette, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney

Meeting date: May 14, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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