CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Vericiguat (VERQUVO)

Indication: Indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent heart failure decompensation event requiring hospitalization and/or IV diuretic therapy. Vericiguat should be used in combination with standard of care therapy for heart failure.

Sponsor: Bayer Inc.

Recommendation: Reimburse with Conditions

Version:	1.0
Publication Date:	May 2023
Report Length:	18 Pages

Single Technology

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that vericiguat be reimbursed for the treatment of symptomatic chronic heart failure (HF) in adult patients with reduced ejection fraction who are stabilized after a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, multicentre, double-blind, randomized placebo-controlled trial (VICTORIA, N = 5,050) demonstrated that treatment with vericiguat when added to dual or triple background HF therapy resulted in added clinical benefit for patients with symptomatic chronic HF with a reduced ejection fraction who are stabilized after a recent HF decompensation event. Compared with placebo, treatment with vericiguat was associated with a statistically significant and clinically meaningful reduction in the hazard of a first event of cardiovascular (CV) death or hospitalization for heart failure (HHF) (HR = 0.90; 95% CI, 0.82 to 0.98). The hazard of total HHF events (first and recurrent) was lower in the vericiguat group relative to placebo in the VICTORIA trial (HR = 0.91; 95% CI, 0.84 to 0.99). Compared to placebo, the hazard of the first event of all-cause mortality or HHF was lower in the vericiguat group (HR = 0.90; 95% CI, 0.83 to 0.98). Patients identified an unmet need for new therapies to treat HF with reduced ejection fraction that were effective and improved their quality of life. CDEC concluded that vericiguat potentially meets some of these needs.

Using the sponsor submitted price for vericiguat and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for vericiguat in combination with background therapy was $62,778 per quality-adjusted life-year (QALY) compared with background therapy alone. Vericiguat is not cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY for adult patients with chronic HF and reduced ejection fraction who are stabilized after a recent HF decompensation event. A price reduction is required for vericiguat to be considered cost-effective at this threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults 18 years and older with symptomatic chronic HF with reduced ejection fraction.	In the VICTORIA trial, treatment with vericiguat demonstrated a clinical benefit in patients who were at least 18 years of age and with symptomatic chronic HF and reduced ejection fraction (LVEF<45%). This aligns with the Health Canada indication for vericiguat for HF.	Vericiguat should be prescribed in combination with standard of care HF therapy.
2. Patients must have a recent HF decompensation event requiring hospitalization and/or IV diuretic therapy.	Patients enrolled in the VICTORIA trial had a recent HF decompensation event, defined as previous HHF within 6 months or IV diuretic treatment for HF (without hospitalization) within 3 months prior to randomization. This aligns with the Health Canada indication for vericiguat for HF.	—
Pricing		
3. A reduction in price	The ICER for vericiguat in combination with BT is $62,778 when compared with BT alone. A price reduction of 14% would be required for vericiguat in combination with BT to achieve an ICER of $50,000 per QALY compared to BT alone.	—
Feasibility of Adoption		
4. Organizational feasibility	Potential exists for vericiguat to be prescribed to patients outside the eligible population for the VICTORIA trial. Consequently, the value represented to the full indicated population is unclear.	—

BT = background therapy; HHF = hospitalization for heart failure; HF = heart failure; ICER = incremental cost-effectiveness ratio; IV = intravenous; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SGLT-2 = sodium-glucose cotransporter-2.

Discussion Points

- CDEC acknowledged that the VICTORIA trial demonstrated that vericiguat can be beneficial in combination with dual or triple HF therapy. In the VICTORIA trial, background therapy included beta blockers, angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), or an angiotensin receptor neprilysin inhibitor (ARNI), and mineralocorticoid receptor antagonists (MRAs). In the VICTORIA trial, 91.4% of patients were receiving at least two medications, 60% of patients were receiving three medications, and 14% of patients were receiving sacubitril/valsartan.
- CDEC identified an evidence gap between the treatment regimens in the VICTORIA trial and current standard quadruple therapy, which includes SGLT-2 inhibitors. No patients received background therapy with SGLT-2 inhibitors in the VICTORIA trial. Therefore, the cumulative benefit and potential harms of adding vericiguat to standard quadruple therapy or adding vericiguat instead of SGLT-2 inhibitors to triple therapy, remains unknown.
- CDEC further noted the cost-effectiveness, incremental benefit and incremental cost of vericiguat either added to standard quadruple therapy or adding vericiguat instead of SGLT-2 inhibitors to triple therapy, remains unknown.
- CDEC noted that there was no evidence from the VICTORIA trial that demonstrated whether patients that are intolerant to one or more of the classes of medications included in standard HF therapy may benefit from the addition of vericiguat.
- The potential misclassification of CV deaths in the VICTORIA trial may overestimate the true incidence by including undetermined cause of death (27% [112 of 414 CV deaths] and 23% [101 of 441 CV deaths] in the vericiguat and placebo groups respectively), and therefore there is a possibility that stopping the trial early may have overestimated the effect of vericiguat compared to placebo. The presence and extent of any overestimation, however, is uncertain.
- In the VICTORIA trial, 26.4% of patients in the trial were screening failures mostly due to below-threshold NT-proBNP levels. The clinical expert consulted indicated that NT-proBNP testing is not widely available in Canada. Thus, this patient selection criterion would be difficult to implement in clinical practice.
- Improvement in health-related quality of life (HRQoL) has been identified by both patients and the clinical expert as an important outcome and goal in the treatment of patients with HF. In the VICTORIA trial, no clinically meaningful differences were found between treatment groups in change from baseline KCCQ scores (less than MID of at least 5 points) and EQ-5D-5L index scores at Week 32. These results should be interpreted as supportive evidence only, as this outcome was not part of the statistical testing hierarchy, and there was a high rate of attrition at later follow-up periods.

Background

Heart failure (HF), sometimes referred to as congestive heart failure, is a clinical condition whereby the heart is unable to adequately pump blood throughout the body to maintain the metabolic needs of tissues and organs. HF results from structural or functional impairment of ventricular filling or ejection of blood. HF is classified based on the percentage of blood that is being pumped out of the left ventricle otherwise known as the left ventricular ejection fraction (LVEF). HF with reduced ejection fraction (HFrEF) is defined as HF with a left ventricular ejection fraction (LVEF) of 40% or less, whereas having an LVEF of 50% or greater is termed HF with preserved ejection fraction (HFpEF). There are an estimated 669,000 people in Canada older than 40 years with HF, with an age-standardized prevalence of 3.5%.3 Between 2001 and 2013, the age-standardized incidence rate of HF in Canada has declined, as has the age-standardized all-cause mortality rate among people living with HF. However, people in Canada older than 40 years with HF are 6 times more likely to die than those without a HF diagnosis. The economic burden due to HF is substantial, with costs associated with health care services, medications and lost productivity.

Common symptoms of HF include dyspnea (breathlessness) and fatigue, exercise intolerance and fluid build-up, which in turn may lead to pulmonary congestion and peripheral edema (mainly feet, ankles or legs), that is significantly affecting their quality of life. Depending on symptoms severity, HF may go unnoticed, only causing minor symptoms, but patients with advanced HF may find it difficult to carry out normal everyday activities. HF leads to a progressive decline in cardiac function over time, with persistent signs and symptoms interspersed with acute episodes of decompensation. Acute decompensated HF is a sudden worsening of the signs and symptoms of HF that often lead to hospitalization or an emergency department visit. Worsening HF and hospitalizations for HF portend a poor prognosis and are associated with an increased risk of mortality and readmissions.6 Hospitalizations due to HF are frequent, with 83% of patients hospitalized at least once, and 43% of patients are hospitalized 4 or more times after a diagnosis of HF. It is generally accepted that hospitalization for acute decompensated HF is a powerful predictor of readmission and death after discharge in patients with chronic HF, with post-discharge mortality rates as high as 20%. The current foundational pharmaceutical management of HF with reduced ejection fraction encompasses combination therapy (in the absence of contraindications), including 1 evidence-based medication from each of the following categories: 1) sacubitril/valsartan, either as first-line therapy or switching from ACEis, or ARBs, 2) beta-blockers, 3) MRAs, and 4) SGLT-2 inhibitors. More recently, new therapies, such as soluble guanylate cyclase stimulator (sGC) or ivabradine (sinus node inhibitor), have emerged to be taken in conjunction with well-established therapies and have shown benefit in HFrEF.

Vericiguat is a stimulator of soluble guanylate cyclase (sGC). HF is associated with impaired nitric oxide (NO) synthesis and decreased activity of its receptor, sGC. Vericiguat restores the relative deficiency in this signaling pathway by directly stimulating sGC, independently and synergistically with NO, to increase the level of intracellular cGMP, which may improve both myocardial and vascular function. According to the proposed Health Canada indication, vericiguat is indicated for the treatment of symptomatic chronic heart failure in adult patients with reduced ejection fraction who are stabilized after a recent heart failure decompensation event requiring hospitalization and/or IV diuretic therapy. VERQUVO should be used in combination with standard of care therapy for heart failure. VERQUVO should be initiated under the supervision of a healthcare professional who is experienced in the management of HF. The recommended starting dose of vericiguat is 2.5 mg administered orally once daily, followed by doubling the dose every 2 weeks to the target maintenance dose of 10 mg, as tolerated by the patient.

Sources of Information Used by the Committee

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

- a review of 1 clinical trial in adult patients with symptomatic chronic HF and reduced ejection fraction
- patients' perspectives gathered by 2 patient groups: the HeartLife Foundation, and the Heart Function Clinic in Vancouver General Hospital, St. Paul's Hospital
- input from public drug plans that participate in the CADTH review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with HF
- input from 3 clinician groups, including Oakville Cardiologists, University of Alberta, Division of Cardiology, and the North Shore Heart Centre

- a review of 4 published indirect treatment comparisons (ITCs) retrieved from the literature
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups, the HeartLife Foundation and the Heart Function Clinic in Vancouver General Hospital, St. Paul's Hospital, provided input for the review of vericiguat. The HeartLife Foundation is a patient-driven Federal Charity whose mission is to transform the quality of life for people living with HF by engaging, educating, and empowering a global community to create lasting solutions and build healthier lives. The input was informed by interviews with 3 HF specialists (British Columbia, Ontario, and Quebec), 1 researcher (Alberta), and 2 patients with HF (British Columbia and Ontario), as well as the review of study material and online literature.

The HeartLife Foundation indicated that patients with HF experience a wide range of physical, social, and emotional challenges. Symptoms include shortness of breath, extreme fatigue, low blood pressure, dizziness, edema, bloating, palpitations, and arrhythmia. The HeartLife Foundation highlighted that access to care, medical therapies, and support services varied widely across Canada and that every individual's experience with HF is unique. Two patient interviews (ages were 33 and 44 years; 1 male and 1 female) highlighted the impact of HF on their quality of life, including being unable to pursue their desired career and exercise regularly. A recurring theme in the 2 patient interviews was the need to find a 'new normal' for life following their diagnosis of HF. The Heart Function Clinic highlighted the following gaps in the treatment of HF: not all patients respond to available treatments, and patients become refractory to existing treatment options. The HeartLife Foundation indicated that patients with HF seek to improve their quantitative and qualitative outcomes. The HeartLife Foundation further emphasized that it is imperative to provide equitable access to high-quality care and services for all patients with HF, including access to diagnostics, medical therapy, mental health support, cardiac rehabilitation, and advanced care. The HeartLife Foundation advocated for vericiguat to be approved for the indication under review and suggested that vericiguat will help alleviate the gaps in current therapy.

Clinician input

Input from the clinical expert consulted by CADTH

The clinical expert consulted by CADTH for this review indicated that HFrEF is still associated with increased rates of death and need for hospitalization despite standard therapy. The clinical expert noted that not all patients are eligible for the standard quadruple therapy due to side effects or comorbidities. It was further highlighted by the clinical expert that some patients who experience disease progression while on standard therapy may require escalation of therapy to become restabilized. The clinical expert consulted indicated that vericiguat can be added to foundational quadruple HF therapy, as its mechanism of action differs from that of the foundational treatment. However, the impact or role of vericiguat in the context of current quadruple therapy is unknown because the VICTORIA trial was designed and completed before the current therapeutic paradigm, that now includes SGLT-2 inhibitors, was widely adopted. The clinical expert consulted indicated that patients included in the VICTORIA trial received foundational therapy and generally tended to be "sicker" than those included in HF trials with other therapies. The clinical expert noted that the response to therapy in clinical practice is assessed based on reduction in burden of symptoms, need for escalation of diuretic therapy, hospitalization, or death. The clinical expert indicated that vericiguat should be prescribed by a practitioner with expertise in the management of HF in specialty clinics with focus in the assessment and management of HF. It was further mentioned by the clinical expert that addition of this medication is expected to have a positive impact on the management of these patients.

Clinician group input

The clinician group input was obtained from 3 clinician groups, including Oakville Cardiologists represented by 9 clinicians, 1 clinician from the Division of Cardiology, University of Alberta, and 1 clinician representing the North Shore Heart Centre. The clinician from the Division of Cardiology, University of Alberta identified the following as key goals of new therapies in heart failure: reducing recurrent symptoms and the need for hospitalization or emergency room visits. All clinician groups agreed that morbidity and mortality remain high in patients with HFrEF despite advancements in therapies, and many patients cannot be titrated to the optimal doses of the medications due to hypotension, hyperkalemia, bradycardia, and renal dysfunction. The clinician groups agreed that vericiguat represents an additional approach to the treatment of HFrEF, which is not targeted by the current guideline-directed medical therapy (GDMT). The clinician from the Division of Cardiology, University of Alberta also suggested that because vericiguat does not cause hyperkalemia or impair renal function, patients who cannot tolerate ARNis or ACEis (e.g., diabetics and renal impaired patients) would be good candidates for vericiguat. The clinical groups pointed out several reasons which may lead to the discontinuation of vericiguat, including a decline in the glomerular filtration rate less than 15 mL/min/1.73 m^2, severe hypotension, and syncope. The Oakville Cardiologists indicated that physician assessment of clinical stability and patient reported symptoms continue to be the cornerstone of evaluating response to therapy in patients with HFrEF in the outpatient setting. The clinical groups advocated for vericiguat to be an accessible treatment option to the high-risk HF patient population as it is safe, well-tolerated, and taken once daily.

Drug Program Input

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	
a) Issues with the choice of comparator in the submitted trial The pivotal phase III VICTORIA trial demonstrated that VERQUVO had a significant reduction in CV death and HHF with a comparable safety profile to placebo on top of background therapy. The background therapy included ACEi/ARB/ARNi, a beta-blocker, and/or MRA, which represent the SOC at the time of trial conclusion and continue to represent fundamental pillars of the new SOC. The Canadian Cardiovascular Society (CCS) defines 4 key therapeutic drug classes as standard therapy for most patients: ARNI (as first-line therapy or after ACEi/ARB titration); beta blockers; MRAs; and SGLT-2 inhibitors. How can vericiguat be integrated into the current treatment paradigm with drugs such as dapagliflozin or empagliflozin, or ivabradine?	Vericiguat may be added to foundational quadruple HF therapy, as its mechanism of action is different from quadruple therapy medications. However, given SGLT-2 inhibitors are also now an option, the cumulative benefit of vericiguat added to quadruple therapy remains unknown. Not all patients are eligible for standard quadruple therapy due to side effects, contraindications, or comorbidities, and vericiguat could be a treatment option for these patients.
Considerations for initiation of therapy	
a) Disease diagnosis, scoring or staging for eligibility In the VICTORIA trial, evidence of worsening HF was categorized based on the timing of the HF decompensation: those hospitalized within 3 to 6 months before randomization, or those receiving IV diuretics for HF, without hospitalization, within the previous 3 months.	HF decompensation event or progressive HF is most commonly defined as worsening symptoms while on conventional therapy, resulting in treatment escalation and hospitalization or outpatient IV diuretic treatment. The laboratory and diagnostic tests to define worsening HF include elevated BNP or NT-proBNP, or reduction in ejection fraction.

Implementation issues	Response
How is worsening HF defined in clinical practice?	
b) Eligibility to re-treatment What is the expected treatment duration for vericiguat?	HF is a chronic disease, and given the mechanism of action of vericiguat, the duration of treatment is indefinite.
Considerations for prescribing of therapy	
a) Dosing, schedule/frequency, dose intensity The recommended starting dose of VERQUVO is 2.5 mg administered orally once daily, followed by doubling the dose every 2 weeks to the target maintenance dose of 10 mg, as tolerated by the patient.	Comment from the drug programs to inform CDEC deliberations.
b) Consistency with prescribing criteria associated with other drugs reviewed by CADTH in the same therapeutic space Per the indication and sponsor request "should be initiated under the supervision of a healthcare professional who is experienced in the management of HF"	Comment from the drug programs to inform CDEC deliberations.
System and economic issues	
a) Concerns regarding the anticipated budget impact and sustainability The List Price of VERQUVO 2.5 mg, 5 mg, and 10 mg is anticipated to be $4.83 per tablet in Canada, which corresponds to a total cost of $4.83 per day (once daily dosage). BIA estimate that listing VERQUVO will lead to an incremental budget impact of $2,469,604 in Year 1, $5,010,977 in Year 2, and $7,625,827 in Year 3 for a total of $15.1 million over three years.	Comment from the drug programs to inform CDEC deliberations.
b) Presence of confidential negotiated prices for comparators Negotiated prices for Inspra (eplerenone), Entresto (sacubitril/valsartan) and Forxiga (dapagliflozin) for HF. Generics available for other comparators.	Comment from the drug programs to inform CDEC deliberations.

AECi = angiotensin-converting enzyme inhibitor; ARNi = angiontensin receptor neprilysin inhibitor; BNP = brain natriuretic peptide; CV = cardiovascular; HF = heart failure; HHF = hospitalization for heart failure; IV = intravenous; NT-proBMP = N-terminal pro-brain natriuretic peptide; MRA = mineralocorticoid receptor antagonist; SOC = standard of care; SGLT-2 = sodium-glucose cotransporter-2.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

The VICTORIA trial was a phase III, randomized, multi-centre, double-blind, event-driven, placebo-controlled trial, designed to assess the efficacy and safety of vericiguat versus placebo as an adjunct to standard of care therapy in adults with symptomatic chronic HF and ejection fraction less than 45% who are stabilized after a recent worsening HF event. Previous HF decompensation (or worsening) was defined as HHF within 6 months prior to randomization or use of intravenous diuretic for HF (without hospitalization) within 3 months prior to randomization. A total of 5,050 patients with symptomatic chronic HFrEF were enrolled across 694 sites in 42 countries in North America (560 patients), Eastern Europe, Western Europe, Asia Pacific, and Latin and South America. The primary efficacy endpoint was the time to first event of the adjudicated CV death or HHF, and the key secondary endpoints were time to CV death, time to first event of HHF, time to total events (first and recurrent) of HHF, time to first event of all-cause mortality or HHF, and time to all-cause mortality. Health-related quality of life (HRQoL) was assessed using the Kansas City

Cardiomyopathy Questionnaire (KCCQ) and EuroQol 5-dimensions (EQ-5D) instrument. A futility and efficacy interim analyses were planned at the time when approximately 75% (587 events) of the planned number of CV death events were reached, and data safety monitoring board could recommend early termination of the trial for overwhelming efficacy or futility. The database lock was executed on October 31, 2019.

Overall, baseline characteristics were well-balanced between treatment groups in the VICTORIA trial. The mean age of all randomized patients in the VICTORIA trial was 67.3 years (SD = 12.2 years), and most patients were male (76.1%), White (64.1%), and non-Hispanic or Latino (81.4%). The mean LVEF was 28.9% (SD = 8.30%), and nearly half of patients had an LVEF of less than 30% (49.3%). Most patients had an NYHA functional class II and III (98.6%) at baseline. The mean N-terminal pro-brain natriuretic peptide (NT-proBNP) was [redacted] pg/mL (SD = [redacted] pg/mL), the mean brain natriuretic peptide (BNP) was [redacted] pg/mL (SD = [redacted] pg/mL), and the mean estimated glomerular filtration rate (eGFR) was [redacted] mL/min/1.73 m^2 (SD = [redacted] mL/min/1.73 m^2). Approximately 70% of patients had HHF within 3 months prior randomization, 30% had HHF within 3 to 6 months, and 15.9% had outpatient treatment with IV diuretics for worsening HF within 3 months prior to hospitalization. A total of 91.4% of patients received 2 or more HF medications, and only 60% of patients received triple therapy, including ACEis or ARBs, beta blockers, and MRAs.

Efficacy Results

Time to first event of CV death or HHF

A composite of time to first event of adjudicated CV death or HHF occurred in 897 patients (35.5%) in the vericiguat group and 972 patients (38.5%) in the placebo group. The annual event rate was lower in the vericiguat group compared to placebo (33.6% and 37.8%, respectively), with a hazard ratio (HR) 0.90 (95% CI, 0.82 to 0.98, P = 0.019) in favour of the vericiguat group. The median follow-up duration was 11.1 months in the vericiguat group and 10.4 months in the placebo group. The proportion of HHF as first event was lower in the vericiguat group (27.4%) compared to placebo (29.6%), while proportion of CV death was similar across the treatment groups (8.2% vs. 8.9% in the vericiguat and placebo groups, respectively).

Time to CV death

This secondary outcome was tested in a non-hierarchical sequence without adjustments for multiplicity and was exploratory in nature. The number of CV death events was 414 (16.4%) in the vericiguat group and 441 (17.5%) in the placebo group. The proportion of patients who died due to HF was 6.5% and 7.6% in the vericiguat and placebo groups, respectively, sudden cardiac event - 4.2% and 4.5% in the vericiguat and placebo groups, respectively, and undetermined cause of death - 4.4% and 4.0% in the vericiguat and placebo groups, respectively. The HR for the time to CV death was 0.93 (95% CI, 0.81 to 1.06, P = 0.269).

Time to all-cause mortality

A total of 512 (20.3%) patients in the vericiguat group and 534 (21.2%) patients in the placebo group died from any cause. The annual event rate was similar across the treatment groups (16.0% and 16.9% in the vericiguat and placebo groups, respectively), with a HR of 0.95 (95% CI, 0.84 to 1.07; P = 0.377).

Time to first event of all-cause mortality or HHF

A composite of time to first event of all-cause mortality or HHF occurred in 957 patients (37.9%) in the vericiguat group and 1,032 patients (40.9%) in the placebo group. The annual event rate was 35.9% and 40.1% in the vericiguat and placebo groups, respectively, with a HR of 0.90 (95% CI, 0.83 to 0.98; P = 0.021). This difference was likely driven primarily by a lower proportion of HHF events, although individual components of this composite endpoint were not formally tested for significance.

Time to CV hospitalization

This secondary outcome was tested in a non-hierarchical sequence without adjustments for multiplicity and was exploratory in nature. A total of [redacted] in the vericiguat group and [redacted] in the placebo group had CV hospitalizations. The annual event rate was lower in the vericiguat group ([redacted]) compared to placebo ([redacted]), with an HR [redacted]

Time to first event of HHF

This secondary outcome was tested as a component of the primary composite endpoint in a non-hierarchical sequence without adjustments for multiplicity and was exploratory in nature. The number of patients with HHF events was 691 (27.4%) in the vericiguat group and 747 (29.6%) in the placebo group. The annual event rate was 25.9% in the vericiguat group and 29.1% in the placebo group, with an HR of 0.90 (95% CI, 0.81 to 1.00; P = 0.048).

Time to total events (first and recurrent) of HHF

The total number of HHF events was lower in patients who received vericiguat (1,223) compared to those who received placebo (1,336). The annual event rate was 38.3% in the vericiguat group and 42.4% in the placebo group, with an HR of 0.91 (95% CI, 0.84 to 0.99; P = 0.023).

Health-related quality of life

No strong conclusions could be drawn about the effect of vericiguat compared with placebo on HRQoL due to an increased risk of type 1 error and a high risk of attrition bias.

KCCQ score

For the analysis of the KCCQ score based on the ITT, Week 32 data were missing for 22.8% to 30.4% of patients in the vericiguat group, and for 23.8% to 32.0% of patients in the placebo group. No clinically meaningful differences were found between the treatment groups in change from baseline in KCCQ scores at Week 32 (less than MID of 5 or more points).

KCCQ overall summary score

KCCQ overall summary score combines the physical limitation, total symptom, social limitation, and health-related quality of life domains into a single score. The analysis showed a slight improvement from baseline of 2.6 points (SD = 28.4) in the vericiguat group and 0.8 points (SD = 30.0) in the placebo group in the KCCQ overall summary score at Week 32, with Least squares (LS) mean difference of 1.2 (95% CI, –0.5 to 2.9; P = 0.180).

KCCQ total symptom score

KCCQ total symptom score combines the symptom burden and symptom frequency domains into a single score. The analysis showed a slight improvement from baseline of [redacted] in the vericiguat group and [redacted] in the placebo group in the KCCQ total symptom score at Week 32, with Least squares (LS) mean difference of [redacted].

KCCQ clinical summary score

KCCQ total symptom score incorporates the combines the physical limitation and total symptom domains into a single score. The analysis showed a slight improvement from baseline of [redacted] in the vericiguat group and [redacted] in the placebo group in the KCCQ clinical summary score at Week 32, with Least squares (LS) mean difference of [redacted].

EQ-5D-5L

For the analysis of the EQ-5D-5L index score based on the ITT, Week 32 data were missing for 23.1% and 24.8% of patients in the vericiguat and placebo groups, respectively. No difference was found between 2 treatment groups in mean change of EQ-5D-5L score at Week 32. For the EQ-5D-5L UK and US index scores, the Least squares (LS) mean differences at Week 32 for vericiguat versus placebo were [redacted] and 0.01 (–0.01 to 0.03; P = 0.257), respectively.

Harms Results

A total of 2,027 (80.5%) patients in the vericiguat group and 2,036 (81.0%) patients in the placebo group experienced 1 or more AE. The most common AEs occurring in the vericiguat or placebo groups were hypotension (15.4% and 14.1%, respectively), cardiac failure (8.9% and 9.9% in the vericiguat and placebo groups, respectively), anemia (7.6% and 5.7%, respectively), and pneumonia (6.4% and 7.2%, respectively). A total of 653 (25.9%) patients in the vericiguat group and 606 (24.1%) patients in the placebo group

experienced 1 or more AE leading to dose modification. The proportion of fatal AEs during the double-blind treatment phase was similar across the treatment groups (3.3% and 3.4% in the vericiguat and placebo groups, respectively). A total of 826 (32.8%) patients in the vericiguat group and 876 (34.8%) in the placebo groups experienced 1 or more SAE. Withdrawal of study treatment due to AEs was required in 167 (6.6%) patients in the vericiguat group and 158 (6.3%) patients in the placebo group. The most common reasons for discontinuation were hypotension (1.9% and 1.3% in the vericiguat and placebo groups, respectively), chronic kidney disease (0.3% and 0.6% in the vericiguat and placebo groups, respectively), pneumonia (0.1% and 0.2% in the vericiguat and placebo groups, respectively), cardiac failure (0.2% and 0.2% in the vericiguat and placebo groups, respectively), and dyspepsia (0.2% and 0.1% in the vericiguat and placebo groups, respectively). In the VICTORIA trial, symptomatic hypotension was the most commonly reported notable AE (9.1% and 7.9% in the vericiguat and placebo groups, respectively), followed by syncope (4.0% and 3.5% in the vericiguat and placebo groups, respectively), and hepatic AEs (0.9% and 0.5% in the vericiguat and placebo groups, respectively).

Critical Appraisal

Internal validity

The VICTORIA trial used accepted methods for blinding, allocation concealment, and randomization with stratification by race and geographic region. An interactive voice response system and integrated web response system methodology were used, and randomization with stratification was performed centrally, which typically has a low risk of bias. The baseline demographic and disease characteristics of patients were generally balanced between the treatment groups, so randomization was successful. A relatively high proportion of patients prematurely discontinued the trial medication (38.7%), while the cause of discontinuations occurred at a similar frequency between the treatment groups. The clinical expert consulted by CADTH for this review noted that the main reason for treatment discontinuation was fatal events, reflecting the natural course of HF. In accordance with the exclusion criteria, patients in the trial were randomized starting 24 hours after intravenous diuretic treatment, and this period may not be enough to achieve clinically stability after a worsening HF event, which may lead to an underestimation or overestimation of the treatment effect. Furthermore, there was no run-in period in the trial to initiate or maintain optimal doses of HF medications to achieve clinical stability after worsening HF. However, the clinical expert consulted noted that sometimes only 1 dose of diuretics is required to achieve clinical stability, and sometimes it takes several days or weeks to become stable.

An independent blinded Clinical Events Committee performed an adjudication of efficacy and safety endpoints a *priori*. The clinical expert consulted indicated that the primary and key secondary outcomes were appropriate for the disease setting. The analyses of primary and key secondary outcomes were conducted using the ITT population, which maintains randomization and minimizes the risk of bias by comparing groups with similar prognostic factors. Both interim and final analyses were planned a *priori* and adequately described; however, the decision was made to cancel the interim analysis because there were more than expected CV death events. Given the potential misclassification of CV deaths, which may overestimate the true incidence of CV death events as they include undetermined cause of death, there is a possibility that the trial was stopped earlier than planned. Therefore, there is a risk that the effect of vericiguat compared to placebo is overestimated, but the presence and extent of any estimation is uncertain.[11-13] Median primary composite endpoint, all-cause survival, total hospitalization for HF, and a composite of all-cause mortality or hospitalization for HF was not estimable because insufficient follow up time had elapsed for these outcomes; thus, the long-term efficacy of vericiguat is unknown. Subgroup analyses were not adjusted for multiplicity and may not have been powered to detect a treatment difference; as such, any inferences or interpretations based on subgroups should be made with caution. While improvement in HRQoL was of primary importance for both patients and physicians, this was an exploratory outcome and was tested outside the statistical testing hierarchy. The KCCQ is generally a valid and reliable questionnaire for HF, while there is no evidence for the validity and reliability of the EQ-5D instrument in patients with HF. Clinical experts consulted indicated that these tools are not commonly used in clinical practice. No strong conclusions could be drawn about the effect of vericiguat compared with placebo on HRQoL due to an increased risk of type I error, and a high risk of attrition bias, especially at longer follow-up.

External validity

In general, the clinical expert consulted by CADTH for this review confirmed that the population of the VICTORIA trial was similar to patients seen in Canadian clinics, and the study results would be generalizable to patients with HF in Canada with some limitations. CADTH was unable to draw conclusions related to patients with NYHA classes of I and IV, since the VICTORIA trials excluded patients who had an NYHA class I, and only a very small proportion of patients who had an NYHA class IV (1.1%). Furthermore, the clinical expert consulted indicated that patients with an NYHA class IV are more likely to be clinically unstable than those with NYHA class II or III. About 26.4% of patients in the trial did not pass the screening, predominantly because patients' NT-proBNP level was below the pre-specified threshold at screening. According to the clinical expert consulted, NT-proBNP testing is not widely available in Canada as some jurisdictions have limited access to it; thus, this patient selection criterion would be difficult to implement in clinical practice. The clinical expert further noted that enrollment of patients with elevated NT-poBNP levels likely created an enriched population in the trial because these patients appeared to be sicker and may benefit more from treatment with vericiguat than the population in the real-world setting. The clinical expert consulted indicated that the population in the VICTORIA trial was younger than the typical adult population in Canada with symptomatic chronic HFrEF (mean age is 75 to 77 years). Most patients were White, and non-Hispanic or Latino, and only 11% of patients were recruited from North America. The clinical expert consulted noted that the lack of representation of Canadian patients does not reduce generalizability of results to Canadian clinical practice.

About 91% of patients in the trial received 2 or more background HF treatment, and only 60% of patients received triple therapy for HF, representing a large majority of patients whose treatment was suboptimal. In addition, a small proportion of patients (14.4%) received sacubitril/valsartan and none of the patients received SGLT-2 inhibitors for the treatment of HF. According to the clinical expert consulted, SGLT-2 inhibitors became available for the treatment of chronic HF with reduced ejection fraction after the VICTORIA trial was conducted (between 2016 and 2019). Therefore, it is unclear whether the population included in the VICTORIA study is reflective of the population that would be eligible for treatment with vericiguat in current Canadian clinical practice. The clinical expert consulted indicated that vericiguat may be added to foundational quadruple HF therapy (including ACEis or ARBs, beta-blockers, MRAs, and SGLT-2 inhibitors), as its mechanism of action is different from quadruple therapy medications. However, the cumulative benefit of vericiguat added to quadruple therapy remains unknown. According to the clinical expert consulted by CADTH for this review, clinicians will choose to prescribe SGLT-2 inhibitors over vericiguat in combination with triple HF therapy unless contraindicated[6], and only after failure of standard quadruple therapy would they prescribe vericiguat to patients who are stabilized after worsening HF.

Indirect Comparisons

No sponsor-submitted NMA was identified for this review. A focused literature search for indirect treatment comparisons (ITCs) dealing with HF was run in MEDLINE All (1946-) on November 9, 2022. No limits were applied to the search. The literature search identified 7 potential citations, of which 4 were included for consideration for the following reasons: a) in the VICTORIA trial, vericiguat was compared to placebo plus standard triple therapy, b) only 14% of patients received sacubitril/valsartan, and c) none of the patients received SGLT-2 inhibitors for HF treatment, as they became available after completion of this trial. Four studies identified through literature search aimed to compare the efficacy of vericiguat in the treatment of patients with HFrEF with SGLT-2 inhibitors, sacubitril/valsartan, ivabradine, and a standard triple therapy, which were considered as comparators in the systematic review protocol.

Aimo et al. (2021) NMA

The NMA was identified from the literature in the publication from Aimo et al. (2021).[14] The objective of the analysis was to compare vericiguat with sacubitril/valsartan, and SGLT-2 inhibitors in the treatment of patients with HFrEF. Databases including PubMed, EMBASE, and clinicaltrials.gov were searched for articles of interest on September 25, 2020. The systematic review included 6 studies for analysis comparing sacubitril/valsartan, vericiguat, or SGLT-2 inhibitors versus SOC therapy. A random-effects network meta-analysis with DerSimonian-Laird estimator, and a fixed-effects model were performed separately for the primary and secondary outcomes of interest. The primary endpoint of interest was a composite of CV death or HHF, and the secondary endpoints included CV death alone, and HHF alone.

The pooled results of the NMA showed for a composite of CV death or HHF, the HR for SGLT-2 inhibitors versus vericiguat and sacubitril/valsartan was 0.83 (95% CI, 0.73 to 0.94) and 0.92 (95% CI, 0.88 to 1.24), respectively. For CV death, the HR for SGLT-2 inhibitors versus vericiguat and sacubitril/valsartan was 0.88 (95% CI, 0.63 to 1.22) and 1.04 (95% CI, 0.88 to 1.24), respectively. For HHF, the HR for SGLT-2 inhibitors versus vericiguat and sacubitril/valsartan was 0.77 (95% CI, 0.66 to 0.89) and 0.87 (95% CI, 0.75 to 1.02), respectively.

De Marzo et al. (2022) NMA

The NMA was identified from the literature in the publication from De Marzo et al. (2022).[15] The objective of the analysis was to compare the efficacy of vericiguat, ivabradine, and SGLT-2 inhibitors in the treatment of patients with HFrEF. Databases including PubMed, EMBASE, SCOPUS, and Cochrane Library databases were searched for articles of interest on November 30, 2020. The NMA comprised both fixed-effects model and random-effects model within a Bayesian framework. The primary endpoint of interest was all-cause death, and the secondary endpoints included CV death, HHF, and all-cause hospitalization. The systematic review included 69 RCTs for all-cause death, 56 RCTs for CV death, 45 RCTs for HHF, and 26 RCTs for all-cause hospitalization.

The results of the NMA showed for the primary endpoint of all-cause death, the HR for ivabradine and SGLT-2 inhibitors versus vericiguat was 0.97 (95% CrI, 0.60 to 1.60) and 0.94 (95% CrI, 0.62 to 1.40), respectively. For CV death, the HR for ivabradine and SGLT-2 inhibitors versus vericiguat was 1.00 (95% CrI, 0.61 to 1.50) and 0.94 (95% CrI, 0.61 to 1.50). For HHF, the HR for ivabradine and SGLT-2 inhibitors versus vericiguat was 0.89 (95% CrI, 0.50 to 1.70) and 0.88 (95% CrI, 0.56 to 1.60). The results for all-cause hospitalizations were not reported, as this information was not available in 63% of the RCTs examined.

Luo et al. (2022)

The NMA was identified from the literature in the publication from Luo et al. (2022).[16] The objective of the analysis was to compare sGCs, ARNI, and SGLT-2 inhibitors in the treatment of patients with HFrEF. Databases including PubMed, EMBASE, Cochrane Library databases, and Web of Science were searched for articles of interest on September 1, 2021. A random-effects model was constructed based on frequency theory. The efficacy outcomes included HF rehospitalization, all-cause mortality, CV death, and CV death or HF rehospitalization. A total of 15 RCTs were included for HF rehospitalization, 14 RCTs for all-cause mortality, 12 RCTs for CV death, and 16 RCTs for CV death or HF rehospitalization.

The results of the NMA for HF rehospitalization, the OR for SGLT-2 inhibitors versus sGCs was 0.79 (95% CI, 0.68 to 0.93), while the OR for ARNI versus sGCs was 0.87 (95% CI, 0.75 to 1.01). For all-cause mortality, the OR for SGLT-2 inhibitors versus sGCs was 0.98 (95% CI, 0.70 to 1.38), while for ARNI versus sCGs was 0.87 (95% CI, 0.61 to 1.25). For CV death, the OR for SGLT-2 inhibitors versus sGCs was 0.96 (95% CI, 0.74 to 1.25), while for ARNI versus sCGs was 0.88 (95% CI, 0.68 to 1.15). For CV death or HF rehospitalization, the OR for SGLT-2 inhibitors versus sGCs was 0.87 (95% CI, 0.76 to 1.00), while for ARNI versus sCGs was 0.88 (95% CI, 0.77 to 1.01).

Pagnesi et al. (2022)

The NMA was identified from the literature in the publication from Pagnesi et al. (2022).[17] The objective of the analysis was to compare vericiguat with SGLT-2 inhibitor in the treatment of patients with HFrEF. Databases including PubMed, EMBASE, Google Scholar, and the Cochrane Central Register of Controlled Trials were searched for articles of interest on March 18, 2021. A random-effects NMA was performed on the cumulative event rates for primary and secondary endpoints based on a frequentist approach with the DerSimonian Laird estimator. The primary endpoint was the composite of CV death or HHF, secondary endpoints were CV death, all-cause death, and HHF. The systematic review included 7 studies for the composite of CV death or HHF, 10 studies for CV death, 12 studies for all-cause mortality, and 10 studies for HHF.

The results of the NMA for a composite of CV death or HHF, the relative risk (RR) for SGLT-2 inhibitor versus vericiguat was 0.84 (95% CI, 0.75 to 0.96). For all-cause mortality, the RR for SGLT-2 inhibitor versus vericiguat was 0.90 (95% CI, 0.77 to 1.04). For CV death, the RR for SGLT-2 inhibitor versus vericiguat was 0.91 (95% CI, 0.91 to 0.96). For HHF, the RR for SGLT-2 inhibitor versus vericiguat was 0.79 (95% CI, 0.69 to 0.91).

Critical appraisal of published NMA articles

The results of the NMA are highly uncertain given the heterogeneity across the studies included in the networks, heterogeneity in the baseline characteristics of patients within the included trials, and limited information related to definitions of endpoints. Furthermore, ivabradine and vericiguat were restricted to selected patients who were stabilized after an episode of worsening HF. Results in efficacy estimates were imprecise (i.e., wide CIs including HR = 1) in many comparisons and endpoints, which adds to the uncertainty in the effect estimates. Therefore, no definitive conclusions can be drawn from the published NMAs for many outcome comparisons due to methodological limitations and impression in the effect estimates. Furthermore, safety outcomes were not analysed in the published NMAs, and no justification was provided, which precludes a balanced judgment of comparative benefits relative to comparative harms. Outcomes important to patients, such as HRQoL, were also not analysed in the published NMAs.

Conclusions

Based on data from the VICTORIA trial, vericiguat demonstrated a statistically significant and clinically meaningful benefit compared to placebo in reducing the hazard rates of first event of CV death or HHF, occurrence of first and recurrent HHF, and the composite of all-cause mortality or HHF in adult patients with symptomatic chronic HFrEF. The median composite primary endpoint, total events of hospitalization for HF, and composite of all-cause mortality or hospitalization for HF were not estimable in either treatment group because insufficient follow up time had elapsed for these outcomes; thus, the longer-term efficacy of vericiguat is unknown. In addition, the estimates of benefit of vericiguat may be overestimated because of the possibility that the trial was stopped earlier than planned due to the potential misclassification of CV death; however, the presence and extent of any overestimation is uncertain. Strong conclusions could not be drawn related to the effect of vericiguat on HRQoL due to the high risk of attrition bias and increased risk of type I error in the analyses of these outcomes. No new safety signals were identified in patients with HFrEF. Owing to its superiority over placebo, vericiguat may be another treatment option for patients with HFrEF who are stabilized after a recent HF decompensation event. According to the clinical expert consulted by CADTH, vericiguat may be added to foundational quadruple HF therapy (including ACEis or ARBs, beta-blockers, MRAs, and SGLT-2 inhibitors); however, the cumulative benefit of vericiguat added to the current modal of quadruple therapy remains unknown. No conclusions could be drawn from the published NMAs about the efficacy of vericiguat relative to SGLT-2 inhibitors, ivabradine, and sacubitril/valsartan, for the treatment of patients with HFrEF due to methodological limitations and imprecision in the effect estimates.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with chronic heart failure (HF) and ejection fraction (EF) <45% who are stabilized after a recent HF decompensation event who (1) are classified as New York Heart Association (NYHA) II to IV chronic HF; and (2) receive concomitant background therapies including: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), angiotensin receptors and neprilysin inhibitors (ARNIs), beta-blockers (BBs), and if tolerated, mineralocorticoid receptor antagonists (MRAs) (aligned with reimbursement request).
Treatment	Vericiguat and background therapies (BT), including ACEIs, ARBs, ARNIs, BBs, and MRAs
Dose Regimen	The recommended starting dose of vericiguat is 2.5 mg once daily. Patients are up-titrated to 5 mg and then to the target dose of 10 mg of vericiguat at 2-week intervals.
Submitted Price	Vericiguat, 2.5 mg, 5 mg, or 10 mg: $4.83 per tablet
Treatment Cost	At the submitted price of $4.83 per 2.5 mg, 5 mg, or 10 mg tablet, the annual per-patient cost of vericiguat is $1,763. This resulted in an annual per-patient cost of $2,567 for vericiguat + BT.
Comparator	BT alone
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	15 years

Component	Description
Key data source	VICTORIA (phase III clinical trial)
Key limitations	• Impact of vericiguat + BT on risk of first heart failure hospitalization (HFH) event is highly uncertain. The sponsor selected joint distributions despite the fact that the VICTORIA trial presented a comparison of therapies with different mechanisms of actions. Moreover, according to clinical experts consulted for the review, all parametric distributions considered by the sponsor for vericiguat + BT yielded five-, 10- and 15- year extrapolations that were deemed optimistic relative to the most plausible extrapolation for BT alone. • Relevant variables were excluded from the risk equations, used in the model, to estimate the risk first HFH event. Clinical experts consulted for the review indicated that the rate of transition to the first HFH event would differ between patients with different levels of chronic obstructive pulmonary disease (COPD), diabetes, smoking status, baseline treatments (i.e., MRAs, ARNIs, devices) and cardiovascular histories. • The sponsor did not incorporate the potential for the waning of treatment effects. Based on the current literature, the efficacy of therapies used to treat heart failure with reduced ejection fraction (HFrEF) could wane as the disease progresses unaffected by treatments. • The population considered in the economic model does not reflect the population of interest. Based on epidemiological evidence, if vericiguat were to become available in clinical practice, the average patient is likely to be 10 years older and receive a different composition of BT. As such, uncertainty exists as to whether the predicted survival benefit will be realized in the real-world setting. • The sponsor omitted sodium-glucose cotransporter-2 inhibitors (SGLT2Is) from the analysis, a relevant drug class for this population, as both empagliflozin and dapagliflozin are components of BT in Canadian clinical practice.
CADTH re-analysis results	• CADTH conducted re-analyses that addressed the uncertainties associated with long-term treatment efficacy by applying alternative parametric extrapolations for the risk of first HFH (vericiguat + BT: gamma; BT alone: Weibull); incorporating linear treatment waning that begins at 2.6 years and ends at 7.6 years; revising the starting cohort mean age to 77 years; and reducing the time horizon to 10 years. • In CADTH's re-analysis, the ICER for vericiguat + BT when compared to BT alone is $62,778 per QALY gained (vericiguat + BT is $8,226 more expensive and yields 0.13 more QALYS) for adult patients with chronic HF and EF<45% who are stabilized after a recent worsening HF event. A price reduction of 14% would be necessary to achieve cost-effectiveness at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained in the reimbursement request population. • The CADTH reanalysis estimated a smaller overall survival (OS) benefit compared to the sponsor's base-case (0.40 incremental LYs in the sponsor's base case vs. 0.16 incremental LYs in CADTH's re-analysis), although uncertainty remains regarding the magnitude. Results should be interpreted carefully, in light of the fact that 80% of the QALY benefit was derived from the period beyond which there is observed trial data. The cost-effectiveness of vericiguat + BT was slightly sensitive to different treatment waning assumptions.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; ARNI = angiotensin receptor and neprilysin inhibitor; BB = beta blocker; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; HF = heart failure; ICER = incremental cost-effectiveness ratio; LY = life-year; MRA = mineralocorticoid receptor antagonist; OS = overall survival; QALY= quality-adjusted life-year; SGLT2I = sodium-glucose cotransporter-2 inhibitors; WTP = willingness-to-pay.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the proportion of patients that would experience a HF decompensation event annually is underestimated, and the proportion of patients with chronic HF and EF less than 45% is uncertain. CADTH performed a reanalysis, in line with clinician expert opinion, by increasing the proportion of patients expected to experience a HF decompensation event annually to 36.8% in accordance with the relevant literature.

Based on the CADTH re-analysis, the budget impact from the introduction of vericiguat is expected to be $2,979,718 in year 1, $6,046,031 in year 2, and $9,200,998 in year 3, with a three-year total of $18,226,748.

CADTH conducted scenario analyses to assess the impact of different assumptions regarding the prevalence of HF with EF<45%. This led to an increase in the estimated 3-year budget impact to $20,728,458 when assuming 58% prevalence and a decrease in the estimated 3-year budget impact to $16,082,424 when assuming 45% prevalence.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: March 23, 2023

Regrets:

One expert committee member did not attend.

Conflicts of interest:

None.