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CADTH Reimbursement Recommendation

Empagliflozin (Jardiance)

Indication: Indicated in adults as an adjunct to standard-of-care therapy for the treatment of chronic heart failure

Sponsor: Boehringer Ingelheim Canada Ltd.

Final recommendation: Reimburse with conditions

CADTH

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Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Jardiance?

CADTH recommends that Jardiance should be reimbursed for the treatment of chronic heart failure as an adjunct to standard-of-care therapy if certain conditions are met.

Which Patients Are Eligible for Coverage?

Jardiance should only be covered to treat patients 18 years and older whose heart is unable to pump enough blood to keep up with the body's needs (heart failure) because the heart is either too weak (heart failure with reduced ejection fraction [HFrEF]) or too stiff (heart failure with preserved ejection fraction [HFpEF]). The patient should either have a slight limitation in physical activity (New York Heart Association [NYHA] functional classification class II) or a marked limitation in physical activity (NYHA class III).

What Are the Conditions for Reimbursement?

Jardiance should only be reimbursed if the price is less costly than dapagliflozin for the treatment of chronic heart failure. Jardiance should be prescribed as an added therapy to standard therapy for chronic heart failure.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that Jardiance reduced the risk of cardiovascular death or hospitalizations for heart failure in patients with chronic heart failure.
- Based on CADTH's assessment of the health economic evidence, Jardiance does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Jardiance compared with dapagliflozin for the treatment of HFrEF.
- Based on public list prices, reimbursement of Jardiance for the treatment of chronic heart failure is expected to cost the public drug plans approximately $170,069,261.

Additional Information

What Is Heart Failure?

Heart failure is a condition whereby the heart is unable to pump enough blood to keep up with the body's needs. Heart failure can be considered acute (no previous signs or symptoms of heart failure) or chronic (slowly over time, the heart weakens and has difficulties pumping enough blood throughout the body). The severity of heart failure is classified in 4 stages, ranging from patients with no heart failure symptoms (NYHA class I) to patients with heart failure symptoms at slight physical activity or even at rest (NYHA class IV).

Unmet Needs in Heart Failure

There are no effective treatments available for patients with chronic HFpEF. Standard-of-care therapy is the only treatment available to these patients; thus, Jardiance (added to standard-of-care therapy) is an option for patients with HFpEF. For patients with HFrEF, Jardiance (added to standard-of-care therapy) can be used as an alternative option to dapagliflozin (added to standard-of-care therapy).

How Much Does Jardiance Cost?

Treatment with Jardiance is expected to cost approximately $1,010 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that empagliflozin be reimbursed for the treatment of chronic heart failure (HF) as an adjunct to standard-of-care (SOC) therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase III, multi-centre, double-blind, randomized, placebo-controlled trials (EMPEROR-Reduced, N = 3,730; EMPEROR-Preserved, N = 5,988) demonstrated that treatment with empagliflozin resulted in added clinical benefit for patients with chronic HF. Both EMPEROR trials demonstrated that, compared with placebo, treatment with empagliflozin (when added to standard pharmacological HF management) was associated with a statistically significant and clinically meaningful reduction in the hazard rate of first event of cardiovascular (CV) death or hospitalization for heart failure (HHF) (EMPEROR-Reduced: hazard ratio (HR)= 0.75; 95% CI, 0.65 to 0.86; EMPEROR-Preserved: HR = 0.79; 95% CI, 0.69 to 0.90). The hazard rate of recurrent HHF was significantly lower in the empagliflozin group relative to placebo in both trials (EMPEROR-Reduced: HR = 0.70; 95% CI, 0.58 to 0.85; EMPEROR-Preserved: HR = 0.73; 95% CI, 0.61 to 0.88). Compared with placebo, the annual rate of decline in the estimated glomerular filtration rate (eGFR) was significantly slower in the empagliflozin group in both trials. [redacted] CDEC concluded that empagliflozin met some of the needs identified by patients — a need for new and effective therapies and greater access to proven therapies — because empagliflozin is an option for patients with HF with preserved ejection fraction (HFpEF) and is an alternative treatment option to dapagliflozin in patients with HF with reduced ejection fraction (HFrEF).

The committee considered exploratory analyses conducted by CADTH, which considered the cost-effectiveness of empagliflozin plus SOC compared with SOC in the HFpEF population and compared with dapagliflozin plus SOC and SOC in the HFrEF population. Using the sponsor-submitted price for empagliflozin and publicly listed prices for all other drug costs, for the HFpEF population NYHA class II subgroup, the incremental cost-effectiveness ratio (ICER) for empagliflozin plus SOC was $13,857 per quality-adjusted life-year (QALY) compared with SOC, whereas for the NYHA class III and IV subgroup, empagliflozin plus SOC was dominated by SOC (empagliflozin plus SOC was more costly and was associated with fewer QALYs). In the HFrEF population, empagliflozin plus SOC was less costly and less effective (associated with fewer QALYs gained) compared with dapagliflozin plus SOC in both the NYHA class II and class III and IV subgroups. Given the high degree of uncertainty associated with the cost-effectiveness of empagliflozin plus SOC due to the sponsor's chosen modelling approach and the lack of comparative clinical evidence compared with dapagliflozin plus SOC, there is no evidence to suggest empagliflozin should be priced higher than dapagliflozin.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must be aged 18 years and older with chronic HF, regardless of LVEF.	Patients in both EMPEROR trials were at least 18 years of age and diagnosed with chronic HF for at least 3 months before entering the trials. The EMPEROR-Reduced trial included patients with LVEF ≤ 40%, whereas the EMPEROR-Preserved trial included patients with LVEF > 40%. This aligns with the Health Canada indication for empagliflozin for HF.	—
2. Patients must be classified as NYHA functional class II or III.	The efficacy of empagliflozin for the treatment of chronic HF was demonstrated primarily in patients with HF classified as NYHA class II or III. Both EMPEROR studies excluded patients classified as NYHA class I and had very few patients classified as NYHA class IV (0.3% to 0.6%).	—
Prescribing		
3. Empagliflozin should be prescribed as an adjunct to standard-of-care therapy.	This aligns with the Health Canada indication for empagliflozin.	—
Pricing		
4. Empagliflozin should be negotiated so that it does not exceed the drug program cost of treatment with dapagliflozin for chronic HF.	CADTH noted that empagliflozin is cost-effective at the submitted price in the HFpEF population but not the HFrEF population. In the HFrEF population, there is insufficient evidence to justify a price premium for empagliflozin over dapagliflozin.	—
Feasibility of adoption		
5. The feasibility of adoption of empagliflozin + standard of care must be addressed.	At the submitted price for empagliflozin, the budget impact of reimbursing empagliflozin is expected to be greater than $40 million in year 2 and year 3. At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimates.	—

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Discussion Points

- Empagliflozin should be prescribed as an adjunct to SOC therapy. The current SOC therapy for HFrEF encompasses foundational "triple therapy," including beta blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs). The clinical experts consulted highlighted that current treatment strategies in HFpEF are limited to supportive therapies focusing on symptom control rather than morbidity or mortality benefit, including ARB, MRA, and angiotensin receptor-neprilysin inhibitor (ARNI), whereas data with sodium-glucose cotransporter-2 (SGLT2) inhibitors show clear benefit in this population.
- Both EMPEROR trials reported a statistically significant difference in the time to first event of adjudicated CV death or HHF in favour of empagliflozin in patients with HF. Although individual components of the composite outcome were not formally tested for significance, this difference was likely driven primarily by reduction of HHF. According to the clinical expert consulted by CADTH, the mean duration of treatment exposure and follow-up period in both trials were likely to be too short to observe a beneficial effect of empagliflozin on mortality.
- The clinical experts consulted by CADTH indicated that clinicians only need to perform N-terminal pro-B-type natriuretic peptide (NT-proBNP) testing in 10% to 20% of cases, when they are unsure of the diagnosis of HF. Thus, NT-proBNP testing can support a HF diagnosis but it is not required.
- Improvement in health-related quality of life (HRQoL) has been identified by both patients and clinical experts as an important outcome and an important goal in the treatment of patients with HF. The results of the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary and total symptom scores were more favourable for empagliflozin compared with placebo in both EMPEROR trials. However, the results should be interpreted as supportive evidence only because this outcome was not part of the statistical testing hierarchy and there was a high rate of attrition at later follow-up periods.
- CDEC recognized that the recommended dose of empagliflozin for the treatment of HF is 10 mg compared with the Health Canada–approved dose of empagliflozin for patients with type 2 diabetes, which is 25 mg or 10 mg. No evidence was identified to suggest that doses greater than 10 mg would provide additional benefit for patients with chronic HF.
- CDEC discussed the results of the sponsor-submitted indirect treatment comparison (ITC) that provided comparative efficacy estimates of empagliflozin plus SOC versus dapagliflozin plus SOC in patients with HFrEF. [redacted]

Background

HF 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. There are an estimated 669,000 people living in Canada older than 40 years of age with HF, with an age-standardized prevalence of 3.5%. Between 2001 and 2013, the age-standardized incidence rate of HF in Canada declined, as did the age-standardized all-cause mortality rate among people living with HF. However, people living in Canada older than 40 years of age with HF were 6 times

more likely to die than those without a HF diagnosis. HFpEF accounts for at least 50% of the patient population with HF, and its prevalence is increasing. Evidence shows that the morbidity and mortality rates for patients with HFpEF were similar or comparable to those for patients with HFrEF. 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), which can significantly affect patients' quality of life. The current pharmacological management of HFrEF includes diuretics, beta blockers, ACE inhibitors or ARBs, as well as MRAs, sacubitril or valsartan, ivabradine, and SGLT2 inhibitors. According to the expert consulted by CADTH, current strategies for the treatment of HFpEF are limited to supportive therapies that focus on symptom control rather than morbidity or mortality benefit, and include ARB, MRA, and sacubitril or valsartan.

Empagliflozin has been approved by Health Canada for use in adults as an adjunct to SOC therapy for the treatment of chronic HF. Empagliflozin is an SGLT2 inhibitor. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. It is available as a 10 mg or 25 mg orally administered tablet. The recommended dosage of empagliflozin for the treatment of chronic HF is 10 mg once daily.

Sources of Information Used by the Committee

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

- a review of 2 clinical trials in adult patients with chronic HF
- a review of 1 sponsor-submitted ITC and 1 published ITC retrieved from the literature
- patients' perspectives gathered by 1 patient group: the HeartLife Foundation
- input from public drug plans that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with HF
- 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 experts consulted by CADTH for the purpose of this review.

Patient Input

The patient and caregiver input received for this review was collected by the HeartLife Foundation, a national charity, which through its extensive network, engages patients and their caregivers to provide education, support, and access to treatments and research. Information for this review was gathered through in-person interviews with 3 patients and 1 caregiver, an online survey of 12 respondents held in April 2022, a closed virtual support group of 11 respondents, and literature searches from peer-reviewed publications.

Patients highlighted the common symptoms of HF, such as shortness of breath, extreme fatigue, low blood pressure, dizziness, edema, and bloating. According to the patient input received, HF has no cure and, if left untreated, will become progressively worse over time. Patients expressed unmet needs for new innovative therapies to improve patient end points for both quantity and quality of life because many patients remain intolerant to beta blockers and in some cases to ACE inhibitors. Respondents expressed a desire to have greater access to proven therapies and improved functional capacity and quality of life to spend time with loved ones and to be able to work on a regular basis, pursue outdoor activities, and travel. There were 16 respondents with experience using empagliflozin who reported that the drug was effective in terms of improving ejection fraction, shortness of breath, and energy level. According the HeartLife Foundation survey (N = 12), approximately 33.3% of respondents felt better after taking empagliflozin, whereas 8.3% reported that they felt worse. Based on the survey results, approximately 33.3% of respondents described their side effects as manageable, whereas 25% described them as not manageable. The frequently reported side effects were fatigue and urinary tract infections.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to the clinical experts consulted by CADTH, many patients with HFrEF are not being assessed by specialists in Canada, and assistance from other specialists is needed given the growing number of patients. The clinical experts further noted that the use of goal-directed, guideline-recommended pharmacological therapy and medical devices in patients with HFrEF remains suboptimal. The clinical experts highlighted that current treatment strategies for HFpEF are limited to supportive therapies that focus on symptom control rather than on morbidity or mortality benefit such as ARB, MRA, and ARNI, whereas data with SGLT2 inhibitors show clear benefit in this population. The clinical experts indicated that empagliflozin can be used as an alternative to dapagliflozin in combination with other goal-directed, guideline-recommended pharmacotherapy in patients with HFrEF, and it is likely to be a first-line therapy for patients with HFpEF because of the ease of use, strength of evidence, safety profile, and familiarity with the use of empagliflozin in patients with type 2 diabetes mellitus. The population least likely to benefit from empagliflozin treatment are patients with low NT-proBNP levels and those classified as NYHA classes I and IV because of limited clinical evidence. The clinical experts indicated that the response to therapy in clinical practice is assessed based on the frequency of HHFs, which in turn may lead to a reduction in mortality, improved quality of life, and a slower decline in kidney dysfunction. The clinical experts further noted that admission for HF is a major cost burden in the health care system. The clinical experts identified the following factors to consider when deciding to discontinue treatment with empagliflozin: the development of severe kidney dysfunction (eGFR < 15 mL/min) and euglycemic diabetic ketoacidosis in patients with diabetes which are important adverse events and classification as NYHA functional class IV. The clinical experts highlighted that empagliflozin is already widely used by primary care providers and endocrinologists for the management of diabetes, by nephrologists to reduce decline in kidney function, and by cardiologists.

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	
Issues with the choice of comparator in the submitted trials: • Only 1 other SGLT2 inhibitor, dapagliflozin, has received approval from Health Canada for the treatment of patients with HFrEF. • Dapagliflozin received a positive recommendation in December 2020 for the treatment of HF in patients classified as NYHA class II or III. Dapagliflozin was originally submitted to CADTH for the treatment of HF in patients classified as NYHA class II, III, or IV. • However, the evidence submitted by the sponsor lacked direct comparison with dapagliflozin as a comparator because it included 2 placebo-controlled trials: ◦ EMPEROR-Reduced which included patients with established HFrEF (LVEF ≤ 40%), with or without type 2 diabetes mellitus ◦ EMPEROR-Preserved which included patients with established HFpEF (LVEF > 40%), with or without type 2 diabetes mellitus.	Comment from the drug programs to inform CDEC deliberations.
[redacted] • If the recommendation is to restrict empagliflozin for the treatment of HF in patients classified as NYHA II or III, which would align with dapagliflozin's CDEC recommendation, is there evidence to support the use of 1 agent over another? • An exclusion criterion in both trials was "current use or prior use of a SGLT2 inhibitor." If the recommendation is to list empagliflozin for the treatment of HF in patients classified as NYHA II, III, or IV, and a patient progresses to NYHA class IV on dapagliflozin, is there evidence to support a switch to empagliflozin? • The sponsor claimed there is a significant need for additional treatment options for both HFrEF and HFpEF. Does CDEC or the clinical experts agree with this statement and, if so, does empagliflozin fit this unmet need?	No head-to-head trials are available for empagliflozin vs. dapagliflozin, but both showed similar benefits in similar populations. There were more similarities than differences in the patient population and findings. There is no clear evidence to support one over the other. The recommendation is to list empagliflozin for the treatment of HF in patients classified as NYHA II or III. There is a need for new and effective therapies and greater access to proven therapies. CDEC agreed with the clinical experts that for HFpEF, this would be in addition to current therapy but, for HFrEF, this would be an alternative agent to dapagliflozin. CDEC acknowledged that the clinical experts noted that there are more studies using SGLT2 inhibitors in progress that are soon to be published.
• The majority of jurisdictions list dapagliflozin for HF or are in the process of listing. • The benefit status and criteria remain consistent; it is listed as a restricted benefit with criteria for the use in patients classified as NYHA class II or III as an adjunct to the standard care of therapy in patients with a LVEF equal or less than 40% • Exceptions include:	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
◦ NIHB, Northwest Territories, Yukon, Canadian Armed Forces, and Corrections Service Canada open benefit ◦ Ontario full benefit with therapeutic notes same as criteria.	
Considerations for prescribing of therapy	
• Based on the existing criteria, there is potential for combination use with empagliflozin and other second-line HF treatments, which include sacubitril and valsartan and/or ivabradine. • Along with the current standard care of therapy, is there evidence to support the combination use of empagliflozin with sacubitril and valsartan and/or ivabradine?	Yes. Patients in both EMPEROR trials received both an ARNI (sacubitril and valsartan class) and ivabradine (in combination with empagliflozin). However, the clinical experts noted that there is likely more evidence to support that a higher number of patients were on sacubitril and valsartan because, typically, ivabradine is only used in patients who cannot tolerate beta blockers or who have not achieved a heart rate of less than 70 bpm with a beta blocker; therefore, the number of patients on ivabradine would be relatively low . From the expert's clinical experience, 1% to 2% of patients were on ivabradine in their practice. Nonetheless, the clinical expert did not foresee the combination use of empagliflozin and sacubitril and valsartan and/or ivabradine as an issue.
System and economic issues	
• There are negotiated confidential prices in place for both dapagliflozin and empagliflozin. • Dapagliflozin has received positive CDEC recommendations for type 2 diabetes and HF, and a rapid response was just published for CKD. • Empagliflozin has received positive CDEC recommendations for type 2 diabetes, high-risk CV disease, and HF. Would having additional indications have an impact on future negotiations?	CDEC agreed with the clinical expert that additional indications would have an impact on future negotiations and acknowledged that the availability of empagliflozin may potentially benefit the payers in terms of price negotiations.

ARNI = angiotensin receptor-neprilysin inhibitor; bpm = beats per minute; CDEC = CADTH Canadian Drug Expert Committee; CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HHF = hospitalization for heart failure; LVEF = left ventricular ejection fraction; NIHB = Non-Insured Health Benefits; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Two phase III, double-blind, placebo-controlled randomized controlled trials (EMPEROR-Reduced and EMPEROR-Preserved) were pivotal trials and included in the systematic review. Both pivotal trials were multi-national, multi-centred, and included Canadian sites. The EMPEROR-Reduced trial (N = 3,730) was designed to assess the superiority of empagliflozin at 10 mg compared with matched placebo as an adjunct to SOC treatment in patient with HF with reduced left ventricular ejection fraction (LVEF ≤ 40%). In the EMPEROR-Reduced trial, the mean age of the patients was 66.8 years (standard deviation [SD] = 11.0 years), 76.1%

were male, 23.9% were female, and the mean LVEF was 27.5% (SD = 6.0), and most patients (75.1%) were classified as NYHA functional class II. The EMPEROR-Preserved trial (N = 5,988) was designed to assess the superiority of empagliflozin at 10 mg compared with matched placebo as an adjunct to SOC treatment in patients with HF with preserved left ventricular ejection fraction (LVEF > 40%). In the EMPEROR-Preserved trial, the mean age of the patients was 71.9 years (SD = 9.4 years), 55.3% were male, 44.7% were female, and the mean LVEF was 54.3% (SD = 8.8), and most patients (81.5%) were classified as NYHA functional class II.

In both EMPEROR trials, the primary efficacy end point was the time to first event of adjudicated CV death or HHF, and the key secondary end points were occurrence of adjudicated HHF (first and recurrent), and eGFR Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine slope of change from baseline. Other secondary and further exploratory outcomes in either trial that were important to the CADTH review included other hospitalization-related and mortality outcomes, as well as patient-reported outcomes, such as HRQoL and HF symptoms assessed by the KCCQ and EQ-5D-5L questionnaires, and functional ability. Harms and notable harms were assessed.

Efficacy Results

Statistical testing in both pivotal trials was conducted based on a hierarchical testing procedure. The following outcomes were controlled for multiplicity in both EMPEROR trials: time to first event of adjudicated CV death or HHF, occurrence of HHF (fist and recurrent), and eGFR (CKD-EPI) creatinine slope of change from baseline. The clinical experts consulted by CADTH for this review indicated that both HHF and CV death are the most important outcomes to assess for treatment response in patients with HF, whereas change in eGFR is not commonly used in clinical practice. Other secondary and further end points were tested in a non-hierarchical fashion without adjustments for multiplicity.

Time to First Event of Adjudicated CV Death or HHF

In the EMPEROR-Reduced trial, a composite of time to first event of adjudicated CV death or HHF occurred in 361 patients (19.4%) in the empagliflozin group and 462 patients (24.7%) in the placebo group. The HR for time to first event of adjudicated CV death or HHF was 0.75 (95% CI, 0.65 to 0.86; P < 0.0001) in favour of the empagliflozin group. Although individual components of the composite primary end point were not formally tested for significance, the proportion of HHFs was lower in the empagliflozin group (13.2%) compared with the placebo group (18.3%), whereas the total proportion of CV deaths was similar across the treatment groups (10.0% versus 10.8% in the empagliflozin and placebo groups, respectively).

In the EMPEROR-Preserved trial, a composite of time to first event of adjudicated CV death or HHF occurred in 415 patients (13.8%) in the empagliflozin group and 511 patients (17.1%) in the placebo group. The HR for time to first event of adjudicated CV death or HHF was 0.79 (95% CI, 0.69 to 0.90; P = 0.0003) in favour of empagliflozin group. The proportion of HHFs was lower in the empagliflozin group (8.6%) compared with the placebo group (11.8%), whereas the total proportion of CV deaths was similar across the treatment groups (7.3% versus 8.2% in the empagliflozin and placebo groups, respectively).

Occurrence of HHF (First and Recurrent)

In the EMPEROR-Reduced trial, the total number of HHFs (first and recurrent) was lower in the group of patients who received empagliflozin compared with those who received placebo (388 and 553, respectively). The hazard rate of recurrent HHFs was significantly reduced in

the empagliflozin group compared with the placebo group (HR = 0.70; 95% CI, 0.58 to 0.85; P = 0.0003).

In the EMPEROR-Preserved trial, the total number of HHFs was lower in patients who received empagliflozin compared with those who received placebo (407 and 541, respectively). The hazard rate of recurrent HHF was significantly reduced in the empagliflozin group compared with placebo (HR = 0.73; 95% CI, 0.61 to 0.88; P = 0.0009).

eGFR Slope of Change From Baseline

In the EMPEROR-Reduced trial, over the double-blind treatment period, the rate of decline in the eGFR (CKD-EPI) creatinine per year was slower in the empagliflozin group (−0.55 mL/min/1.73 m^2 per year; 95% CI, −0.99 to −0.10) than in the placebo group (−2.28 mL/min/1.73 m^2 per year; 95% CI, −2.73 to −1.83), with a between-group difference in slope of 1.73 per year (95% CI, 1.10 to 2.37; P < 0.0001).

[redacted] with a between-group difference in slope of 1.36 per year (95% CI, 1.06 to 1.66; P < 0.001).

Health-Related Quality of Life and Heart Failure Symptoms

Both the patients and clinical experts consulted highlighted patient-reported end points as important outcomes and important treatment goals for patients. However, the interpretation of the results must be made with caution because multiplicity was not controlled for in the analyses of the KCCQ scores.

KCCQ Clinical Summary Score

In the EMPEROR-Reduced trial, the analysis based on the randomized set showed a smaller decline from baseline of −1.30 points (standard error [SE] = 0.69) in the empagliflozin group than in the placebo group (−3.36 points; SE = 0.69) for the KCCQ clinical summary score at week 52, with an adjusted mean difference of 2.06 (95% CI, 0.16 to 3.96) favouring empagliflozin. A responder analysis showed that, at week 52, 40.0% of patients in the empagliflozin group reported at least a 5-point increase in KCCQ clinical summary scores compared with placebo (35.9%) (odds ratio [OR] = 1.23; 95% CI, 1.05 to 1.45).

[redacted]

KCCQ Total Symptom Score

[redacted]

[redacted]

[redacted]

Harms Results

Adverse Events

In the EMPEROR-Reduced trial, 1,420 (76.2%) patients in the empagliflozin group and 1,463 (78.5%) patients in the placebo group experienced at least 1 adverse event (AE). Patients in the empagliflozin and placebo groups experienced treatment-emergent AEs (TEAEs) at a similar frequency (15.2% and 12.2%, respectively). The most common TEAEs that occurred in at least 0.5% of patients in the empagliflozin and placebo groups were hypotension (2.3% and 1.8%, respectively), renal impairment (1.4% and 1.1%, respectively), urinary tract infection (1.4% in each group), and [redacted]

In the EMPEROR-Preserved trial, 2,574 (85.9%) patients in the empagliflozin group and 2,585 (86.5%) patients in the placebo group experienced at least 1 AE. [redacted]

In the EMPEROR-Reduced trial, 772 (41.4%) patients in the empagliflozin group and 896 (48.1%) patients in the placebo group experienced at least 1 serious AE (SAE). In the EMPEROR-Preserved trial, 1,436 (47.9%) patients in the empagliflozin group and 1,543 (51.6%) patients in the placebo group experienced at least 1 SAE.

Withdrawals Due to Adverse Events

In the EMPEROR-Reduced trial, the overall frequency of AEs leading to treatment discontinuation was similar between the treatment groups in both pivotal trials (17.3% and 17.6% in the empagliflozin and placebo groups in the EMPEROR-Reduced trial and [redacted] The most frequently reported types of withdrawals due to AEs in both trials were cardiac failure, death, acute myocardial infarction, renal impairment, and urinary tract infection.

Mortality

[redacted]

Notable Harms

The frequency of notable harms identified in the protocol were comparable between the treatment groups.

In both EMPEROR trials, acute renal failure was the most commonly reported notable AE (empagliflozin versus placebo: 9.4% versus 10.3% in EMPEROR-Reduced and 12.1% versus 12.8% in EMPEROR-Preserved), followed by hypotension (empagliflozin versus placebo: 9.4% versus 8.7% in EMPEROR-Reduced and 10.4% versus 8.6% in EMPEROR-Preserved), urinary tract infection (empagliflozin versus placebo: 4.9% versus 4.5% in EMPEROR-Reduced, and 9.9 versus 8.1% in EMPEROR-Preserved), and bone fracture (empagliflozin versus placebo: 2.4% versus 2.3% in EMPEROR-Reduced and 4.5% versus 4.2% in EMPEROR-Preserved). No new safety concerns were identified.

Critical Appraisal

Internal Validity

Both the EMPEROR-Reduced and EMPEROR-Preserved trials appeared to have acceptable methods for blinding, allocation concealment, and randomization with stratification. For both EMPEROR trials, a computer-generated block randomization scheme was used, and randomization with stratifications was performed centrally, which typically has a low risk of bias. The demographic and baseline patient characteristics appeared to be generally balanced between the treatment groups in both trials, so randomization was maintained. Both EMPEROR trials included only patients with elevated NT-proBNP because high concentrations of NT-proBNP can confirm HF in patients who present with dyspnea when the clinical diagnosis remains uncertain. However, the clinical experts consulted by CADTH highlighted that physicians only need to perform NT-proBNP tests in 10% to 20% of cases, when they are unsure of the diagnosis of HF. A relatively high proportion of patients prematurely discontinued the trial medication (26.7% and 31.5% in the EMPEROR-Reduced and EMPEROR-Preserved trials, respectively, including fatal events), although the cause of discontinuations occurred at a similar frequency between the treatment groups. The clinical experts noted that a high proportion of AEs leading to treatment discontinuation were fatal, which reflects the natural history of HF more than intolerance to the drug under review. An independent, blinded clinical expert committee performed a central adjudication of the primary and key secondary outcomes based on criteria defined a priori. The clinical experts consulted indicated that CV death and HHF are the main outcomes used in clinical practice to assess the response to HF treatment. Although improvement in HRQoL, HF symptoms, and functional ability were of primary importance to patients with HF according to the patient group input, these were exploratory outcomes and were outside the statistical testing hierarchy; thus, the results should be viewed as supportive evidence for the overall effect of empagliflozin. The symptoms associated with HF and HRQoL were assessed using the KCCQ and EQ-5D-5L instruments. The clinical experts indicated that these tools are not used in clinical practice, but are used in multiple studies, which allows for comparisons between different treatments. Treatment discontinuation rates were relatively high across both treatment groups and many patients did not complete the KCCQ or EQ-5D-5L at baseline or follow-up; therefore, there is a high risk of bias because patients who completed the questionnaires may be fundamentally different than those who did not complete (e.g., differences in treatment response, AEs). Assessment of functional ability was based on the change in NYHA functional class from baseline at week 52 using descriptive statistics. The evidence on the use of empagliflozin in patients with chronic HF was limited by 2 placebo-controlled pivotal trials; no head-to-head evidence of empagliflozin compared with other comparators, including dapagliflozin or sacubitril or valsartan in the HFrEF population, were available for this review.

External Validity

In general, the clinical experts consulted by CADTH for this review confirmed that the populations of both the EMPEROR-Reduced and EMPEROR-Preserved trials were similar to patients seen in Canadian clinics, and the study results would be generalizable to patients with HF in Canada with some limitations. Although empagliflozin has been approved by Health Canada for use as an adjunct to SOC therapy in patients with chronic HF regardless of NYHA classification, CADTH was unable to draw conclusions related to patients classified as NYHA functional classes I and IV because both trials excluded patients who were classified as NYHA class I and there was a very small proportion of patients who were classified as NYHA class IV. One of the clinical experts consulted highlighted that the benefit of empagliflozin in patients who are classified as NYHA class IV is unclear because of limited

clinical data and high mortality rates, whereas another clinical expert indicated that he would prescribe empagliflozin to patients with a classification of NYHA class IV. In addition, the clinical experts indicated that they would not prescribe empagliflozin to patients with chronic HF with classifications of NYHA class I because these patients are asymptomatic, which is consistent with the reimbursement request. Approximately 48% of patients in both trials failed screening, most commonly because their NT-proBNP levels were below the pre-specified thresholds at screening, which further reduces the generalizability of the results. The clinical experts consulted indicated that NT-proBNP testing is not widely available in Canada because some jurisdictions have limited access to it; thus, this patient selection criterion would be difficult to implement in clinical practice. The clinical experts further noted that this inclusion criterion likely created an enriched patient population in both trials, and patients with elevated NT-proBNP appeared to be sicker in these trials and could benefit more from treatment with empagliflozin than the population in the real-world setting. In the EMPEROR-Preserved trial, approximately 33% of patients had mid-range LVEF (41% to 49%); however, the clinical experts did not expect this to be a major issue with the generalizability of the trial results because the LVEF definition is arbitrary and estimates of LVEF may vary depending on the patient or technical factors as well as clinical deterioration. The clinical experts consulted noted that the patients included in both EMPEROR trials were younger because the median age of the population of patients with HF in real-world settings is approximately 75 years. The generalizability of the EMPEROR-Reduced trial results may be compromised by the high proportion of males (more than 75%) who were enrolled because half of the population with HFrEF in Canada is female. Nonetheless, the clinical experts consulted noted that they would treat both male and female patients with chronic HF with empagliflozin. The majority of patients in both EMPEROR trials were receiving guideline-recommended treatment for HF, thus they represent patients who are optimally managed, whereas the clinical experts noted that goal-directed treatment of HF is suboptimal in clinical settings. Last, although the recommended dose of empagliflozin for the treatment of HF is 10 mg, the clinical experts indicated that both doses of empagliflozin at 10 mg and 25 mg are used in clinical practice.

Indirect Comparisons

Description of Studies

In the absence of direct comparative evidence from trials, the aim of the ITC conducted according to the methodology described by Bucher et al. (1997), was to compare the efficacy of empagliflozin plus SOC in patients with HFrEF versus dapagliflozin plus SOC in patients with HFrEF. The sponsor chose to restrict the ITC to the 2 pivotal phase III trials for each drug. These represented the studies that were submitted for the purposes of regulatory approval and were the 2 studies with the largest sample size for each drug, the EMPEROR-Reduced and DAPA-HF trials. Both the EMPEROR-Reduced and DAPA-HF trials were phase III, double-blind, multi-centre studies comparing SOC to either empagliflozin or dapagliflozin, respectively. The mean duration of follow-up was slightly longer in the DAPA-HF trial (18.2 months) compared with the EMPEROR-Reduced trial (16 months). The inclusion criteria were similar except in the EMPEROR-Reduced trial higher baseline NT-proBNP and eGFR filtration rates were allowed according to the study inclusion criteria. The primary end point in the EMPEROR-Reduced trial was time to first HHF or CV death, whereas in DAPA-HF, this composite end point also included urgent HF visits. [redacted]

Efficacy Results

[redacted]

Critical Appraisal

The sponsor conducted a Bucher ITC that compared empagliflozin with dapagliflozin in patients with HFrEF. Studies were identified from a systematic review; however, the included studies from the systematic review were further refined on an ad hoc basis to arrive at the 2 pivotal trials for each drug that were analyzed in the ITC, potentially introducing selection bias. The Bucher methodology for ITC assumes all differences in patient characteristics or study design have no impact on treatment effects and estimates relative treatment effects using the common comparator arm of 2 treatments that have not been investigated in a head-to-head study. Important differences between the EMPEROR-Reduced and DAPA-HF trials included a broader primary composite end point in the DAPA-HF trial (the impact of which is uncertain), baseline characteristics indicating sicker patients were included in the EMPEROR-Reduced trial which potentially biased the results in favour of empagliflozin, and a more effective basket of background SOC therapies used in the EMPEROR-Reduced trial which potentially biased results against empagliflozin. [redacted]

An additional 2 ITCs were identified from the literature search conducted by CADTH. Given the lack of details provided, the results were highly uncertain; however, the results indicated no difference between empagliflozin and dapagliflozin and were consistent with the [redacted] opinion of the clinical experts consulted.

Other Relevant Evidence

In addition to the pivotal trials, EMPEROR-Reduced and EMPEROR-Preserved, the following studies were considered relevant studies for this report: the EMPERIAL-Reduced and EMPERIAL-Preserved trials. The CADTH review team identified 2 phase III, multi-centre, randomized, double-blind, placebo-controlled trials that met systematic review inclusion criteria. The CADTH review team did not include the EMPERIAL-Reduced and EMPERIAL-Preserved studies because 1 of the outcomes of interest, KCCQ score, was considered exploratory because the primary end point was not met in the 2 trials. Therefore, although the EMPERIAL-Reduced and EMPERIAL-Preserved studies were not included in the main report, the CADTH review team summarized and appraised the studies to provide additional supportive evidence for KCCQ scores and safety.

Description of Studies

EMPERIAL-Reduced Trial

The effect of empagliflozin on exercise ability and HF symptoms in patients with chronic HFrEF (EMPERIAL-Reduced) trial was a phase III, multi-centre, randomized, double-blind, placebo-controlled study that aimed to evaluate the effect of empagliflozin (10 mg once daily) on exercise capacity and patient-reported outcomes compared with placebo in patients with HFrEF (defined as LVEF ≤ 40%), with or without type 2 diabetes mellitus. A total of 312 patients were enrolled across 109 sites from 8 countries in USA, Canada, Australia, and

Europe. Patients were randomized in a 1:1 ratio to receive either empagliflozin at dose of 10 mg once daily (n = 156) or matching placebo (n = 156) in a double-blind manner. Among these 312 patients, the mean age was 69.0 years (SD = 10.2 years), and the majority of patients were male (74.4%) and White (84.3%). The cause of HF was ischemic in 50.6% (n = 158) of participants, the mean LVEF was 30.3% (SD = 6.7%), and diabetes was present in 59.9% (n = 187) of patients. The study was funded by Boehringer Ingelheim.

EMPERIAL-Preserved Trial

The effect of empagliflozin on exercise ability and HF symptoms in patients with chronic HFpEF (EMPERIAL-Preserved) trial was a phase III, multi-centre, randomized, double-blind, placebo-controlled study that aimed to evaluate the effect of empagliflozin (10 mg once daily) on exercise capacity and patient-reported outcomes compared with placebo in patients with HFpEF (defined as LVEF > 40%) with or without type 2 diabetes. A total of 315 patients were enrolled across 108 sites from 8 countries in USA, Canada, Australia, and Europe. Patients were randomized in a 1:1 ratio to receive either empagliflozin at dose of 10 mg once daily (n = 157) or matching placebo (n = 158) in a double-blind manner. Among these 315 patients, the mean age was 73.5 years (SD = 8.8 years), and the majority of patients were male (56.8%) and White (87.3%). The cause of HF was ischemic in 50.6% (n = 158) of participants, the mean LVEF was 53.1% (SD = 8.0%), and diabetes was present in 51.1% (n = 161) of patients. The study was funded by Boehringer Ingelheim.

Efficacy Results

The primary end point was change from baseline in 6-minute walk test distance (6MWTD) at week 12. Key secondary end points were change from baseline in KCCQ total symptom score and Chronic Heart Failure Questionnaire Self-Administered Standardized format (CHQ-SAS) dyspnea score at week 12. Results for KCCQ total symptom score and CHQ-SAS dyspnea score are presented in accordance with the protocol for the CADTH review. The median difference from baseline to week 12 between empagliflozin and placebo for KCCQ total symptom score was 3.13 (95% CI, 0.00 to 7.29) and 2.08 (95% CI, −2.08 to 6.25) in the EMPERIAL-Reduced and EMPERIAL-Preserved trials, respectively. The median difference between empagliflozin and placebo for CHQ-SAS dyspnea score was 0.10 (95% CI, −0.20 to 0.40) and −0.07 (95% CI, −0.35 to 0.20) in the EMPERIAL-Reduced and EMPERIAL-Preserved trials, respectively. The results for other symptom outcomes are presented in the Other Relevant Evidence section.

Harms Results

There was no notable difference between empagliflozin and placebo for overall frequencies of any AE or any AE leading to treatment discontinuation in both trials. SAEs were reported less frequently with empagliflozin than placebo in the EMPERIAL-Reduced (empagliflozin 12.7% versus placebo 18.4%) and EMPERIAL-Preserved (empagliflozin 13.5% versus placebo 17.3%) trials. Decreased kidney function was reported with similar frequencies in both groups. No ketoacidosis or confirmed hypoglycemic events occurred in participants who did not have type 2 diabetes. No new safety concerns were identified.

Critical Appraisal

The following limitations were identified: HF is a chronic condition, meaning HF is generally slow in progression and the assessment of change in outcomes may require a long-term follow-up period. The follow-up period of the EMPERIAL-Reduced and EMPERIAL-Preserved trial was 12 weeks, which may not be sufficient to assess meaningful changes in the

outcome measures. In addition, the EMPERIAL trials were powered to detect an improvement of 30 m in the 6MWT; however, the study sample size may not have been sufficient enough to detect any between-group changes that were less than 30 m. In addition, because the primary end point — change from baseline in distance in the 6MWT at week 12 — was not met, the analyses of all secondary outcomes, such as KCCQ total symptom score and CHQ-SAS dyspnea score, were considered exploratory. Although the changes in KCCQ total symptom score and CHQ-SAS dyspnea score may suggest a possible favourable effect of empagliflozin in patients with HFrEF, these results are considered exploratory. The baseline demographic and baseline characteristics (sex and 6MWD) were suggestive of an over-representation of male patients with lower functioning status and may compromise the representativeness of the study sample to the general adult patients with HF. Although the EMPERIAL studies provides additional data on the effectiveness and safety of empagliflozin in patients with HF, the limitations identified introduce uncertainty.

Conclusions

Overall, the efficacy of empagliflozin for use in adults as an adjunct to SOC therapy for the treatment of chronic HF has been demonstrated. Based on the EMPEROR-Reduced and EMPEROR-Preserved trials, empagliflozin was significantly more efficacious than placebo in reducing the hazard rate of first event of adjudicated CV death or HHF, as well as occurrence of adjudicated first and recurrent HHF. The annual rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group in both pivotal trials. The benefit of empagliflozin on patient-valued outcomes, such as HRQoL, functional ability, and symptoms associated with HF, should be viewed as supportive evidence only for the overall effect of empagliflozin. The evidence of empagliflozin in patients with chronic HF was limited by 2 placebo-controlled pivotal trials, and no head-to-head evidence of empagliflozin compared with other relevant comparators, including dapagliflozin, sacubitril or valsartan, and ivabradine, in the HFrEF population, were available for this review. The median durations of the EMPEROR-Reduced and EMPEROR-Preserved trials were 1.31 years and 2.15 years, respectively. Thus, long-term efficacy and safety in patients with chronic HF is uncertain. Although empagliflozin has been approved by Health Canada for use as an adjunct to SOC therapy in patients with chronic HF regardless of NYHA class, CADTH was unable to draw conclusions related to patients classified as NYHA functional classes I and IV because both pivotal trials excluded patients who were classified as NYHA class I, and there was a very small proportion of patients who were classified as NYHA class IV. No new safety signals were identified in patients with HFrEF or HFpEF. [redacted]

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model

Component	Description
Target populations	Patients with reduced or preserved ejection fraction heart failure, aligned with the population of the EMPEROR-Reduced and EMPEROR-Preserved trials: • HFrEF: adults with chronic heart failure (functional class II, III, or IV) with left ventricular ejection fraction (LVEF) ≤ 40% • HFpEF: adults with diagnosed symptomatic chronic heart failure (NYHA functional class II, III, or IV) with a LVEF > 40%
Treatments	EMPA + SOC (comprised of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists, beta blockers, and/or ivabradine)
Submitted price	EMPA, 10 mg or 25 mg: $2.77 per tablet
Treatment cost	HFrEF: • SOC: $1,781 annually • DAPA + SOC: $2,778 (DAPA alone = $997) annually • EMPA + SOC: $2,791 (EMPA alone = $1,010) annually HFpEF: • SOC: $259 annually • EMPA + SOC: $1,270 (EMPA alone = $1,010) annually
Comparators	HFrEF: DAPA + SOC; SOC HFpEF: SOC
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (33.08 years for HFrEF; 28.08 years for HFpEF)
Key data source	Effectiveness of EMPA + SOC informed by the EMPEROR-Reduced trial (HFrEF) and the EMPEROR-Preserved trial (HFpEF); comparative clinical efficacy data for EMPA + SOC vs. DAPA + SOC in the HFrEF population were derived from a sponsor-submitted ITC
Key limitations	• The full Health Canada population was not captured in the clinical trials because patients classified with NYHA class I heart failure were excluded. The sponsor's reimbursement request and the modelled population do not reflect the proposed Health Canada indication for EMPA. • The model structure, based on the baseline KCCQ-CCS scores of patients from the EMPEROR-Reduced and EMPEROR-Preserved trials, was divided into quartiles which does not adequately reflect heart failure in clinical practice and does not represent homogenous heart failure health states. This modelling approach prevented CADTH from fully validating the sponsor's model and, if validation was possible, the results were inconsistent with observations from the clinical trials. • Based on heterogeneity in the target populations, analyses stratified by NYHA class should be the primary analysis (i.e., NYHA class II, class III and IV). Scenario analyses by NYHA class were conducted by the sponsor but omitted key comparators (i.e., DAPA + SOC in the HFrEF population). • The comparative efficacy between EMPA + SOC and DAPA + SOC in HFrEF is uncertain owing to a lack of head-to-head trials. The sponsor's ITC suggests [redacted]. Adverse events and treatment discontinuation were not considered in the sponsor's ITC and were assumed to be equal between EMPA + SOC and DAPA + SOC without adequate justification. • The long-term clinical efficacy of EMPA in heart failure is unknown. Further, in the HFrEF group, the sponsor assumed that the movement of patients between health states after the first year of

Component	Description
	treatment would be equivalent for EMPA + SOC and DAPA + SOC, without adequate justification. • No impact on all-cause or cardiovascular mortality was observed in the EMPEROR-Reduced or EMPEROR-Preserved trials, and the sponsor's model may overestimate the survival of patients with heart failure. CADTH was unable to validate the sponsor's mortality estimates owing to the model structure. • The health state utility values derived from the EMPEROR-Reduced and EMPEROR-Preserved trials are uncertain owing to the methodological approaches used by the sponsor. CADTH was unable to validate the utility values owing to the model structure.
CADTH reanalysis results	• CADTH undertook an exploratory reanalysis stratified by NYHA class subgroup. CADTH was unable to address the remaining limitations noted in Key Limitations. Results of the CADTH exploratory reanalysis suggest that: • Among patients with HFrEF: ◦ In the NYHA II subgroup, EMPA + SOC was associated with an ICER of $5,009 per QALY compared with SOC (incremental costs: $539; incremental QALYs: 0.11). When compared with DAPA + SOC, EMPA + SOC was associated with lower costs (incremental cost: −$1,661) but lower QALYs (incremental QALYs: −0.15), such that EMPA + SOC would not be the optimal treatment strategy if a decision-maker's WTP threshold was greater than $11,081 per QALY. ◦ In the NYHA III and IV subgroup, EMPA + SOC was associated with an ICER of $8,883 per QALY compared with SOC (incremental costs: $3,568; incremental QALYs: 0.40). Compared with DAPA + SOC, EMPA + SOC was less costly and less effective (incremental cost: −$2,018; incremental QALYs: −0.15), such that EMPA + SOC would not be the optimal strategy if a decision-maker's WTP threshold was greater than $13,206 per QALY. • Among patients with HFpEF: ◦ In the NYHA II subgroup, EMPA + SOC was associated with an ICER of $13,857 per QALY compared with SOC (incremental costs: $3,094; incremental QALYs: 0.22). At a WTP of $50,000 per QALY, there was an 80% chance of EMPA + SOC being optimal. ◦ In the NYHA III and IV subgroup, EMPA + SOC was associated with lower QALYs (incremental QALYs: −0.23) and higher costs (incremental costs: $540) when compared with SOC (dominated).

DAPA = dapagliflozin; EMPA = empagliflozin; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICER = incremental cost-effectiveness ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; QALY = quality-adjusted life-year; SOC = standard of care; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The modelled population does not reflect the full Health Canada indication for empagliflozin because patients with HF classified as NYHA class I were excluded from the sponsor's analysis. Similarly, the sponsor excluded patients aged 40 years and younger, which is inconsistent with the Health Canada indication.
- The sponsor likely underestimated the size of the eligible population by overestimating the proportion of patients with HF with concurrent type 2 diabetes who are currently prescribed an SGLT2 inhibitor as part of their diabetes management.
- Uptake of empagliflozin in the HFpEF population is expected to be higher than estimated by the sponsor.
- Discrepancies were noted in the unit price of dapagliflozin between the prices used in the sponsor base case and the formulary list prices for some jurisdictions.

- CADTH reanalyses assumed that not all patients with HF and type 2 diabetes currently receive an SGLT2 inhibitor, adopted a higher uptake of empagliflozin in the HFpEF population, and corrected the price of dapagliflozin. CADTH reanalyses suggest that the overall budget impact to the public drug plans of introducing empagliflozin for the treatment of HF is $170,069,261 over 3 years (year 1: $27,951,856; year 2: $48,762,219; year 3: $93,355,187).

The estimated budget impact is sensitive to assumptions about the number of patients eligible for empagliflozin and the proportion of patients currently receiving an SGLT2 inhibitor for the treatment of type 2 diabetes. Should patients classified with NYHA class I be prescribed empagliflozin, the budget impact of reimbursing empagliflozin will be higher than the CADTH base case.

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: August 24, 2022

Regrets: 2 expert committee members did not attend

Conflicts of interest: None