CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Confidential, Draft)

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.

Recommendation: Reimburse with Conditions

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Single Technology

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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.

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 therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase III, multicentre, double-blind, randomized placebo-controlled trials (EMPEROR-Reduced, N = 3730, and EMPEROR-Preserved, N = 5988) 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 heart failure 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) (HR = 0.75; 95% CI, 0.65 to 0.86, and HR = 0.79; 95% CI, 0.69 to 0.90, in EMPEROR-Reduced and EMPEROR-Preserved, respectively). The hazard rate of recurrent HHF was significantly lower in the empagliflozin group relative to placebo in both trials (HR = 0.70; 95% CI, 0.58 to 0.85, and HR = 0.73; 95% CI, 0.61 to 0.88, in EMPEROR-Reduced and EMPEROR-Preserved, respectively). 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. Results from an indirect treatment comparison (ITC) suggest that there is no difference between empagliflozin and dapagliflozin with respect to reducing CV mortality or HHF in patients with HF with reduced ejection fraction. 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 given that empagliflozin is an option for patients with HF with preserved ejection fraction, and is an alternative treatment option to dapagliflozin in patients with HF with reduced ejection fraction.

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

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 left ventricular ejection fraction (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. EMPEROR-Reduced included patients with LVEF ≤ 40%, while EMPEROR-Preserved included patients with with LVEF > 40%. This aligns with the HC indication for empagliflozin for HF.	—
2. Patients must have NYHA functional class II or III	The efficacy of empagliflozin for the treatment of chronic HF was demonstrated primarily in patients with HF with NYHA class II or III. Both EMPEROR studies excluded patients with NYHA class I, and had very few patients with NYHA class IV (0.3% to 0.6%).	—
Pricing		
2. Empagliflozin should be negotiated so that it does not exceed the drug program cost of treatment with dapagliflozin for chronic HF	There is insufficient evidence to justify a price premium for empagliflozin over dapagliflozin for adults with chronic heart failure.	—
Feasibility of Adoption		
3. The feasibility of adoption of empagliflozin + standard of care must be addressed	At the submitted price for empagliflozin, the budget impact of empagliflozin + standard of care 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 estimate(s).	—

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CV = vardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; HHF = hospitalization for heart failure; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT–proBNP = N-terminal pro hormone B-type natriuretic peptide; NYHA = New York Heart Association.

Discussion Points

- Empagliflozin should be prescribed as an adjunct to standard of care therapy. The current standard of care therapy encompasses foundational 'triple therapy', including beta-blockers, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and mineralocorticoid receptor antagonist (MRA).
- 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 that clinicians only need to perform NT–proBNP testing in 10-20% of cases, when they are unsure of the diagnosis of HF. Thus, NT–proBNP testing can support a HF diagnosis, but is not required.
- Improvement in health-related quality of life 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 score were favorable for empagliflozin relative to placebo in both EMPEROR trials. However, the 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.
- CDEC recognized that the recommended dosage of empagliflozin for the treatment of HF is 10 mg as compared to the Health Canada-approved dose of empagliflozin at 25 mg for patients with type 2 diabetes mellitus and established cardiovascular disease. No evidence was identified to suggest that doses beyond 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 standard of care (SOC) versus dapagliflozin plus SOC in patients with HF with reduced ejection fraction. Results of the submitted ITC showed no differences between empagliflozin and dapagliflozin in terms of reducing CV mortality, HHF, all-cause mortality, and time to worsening renal function in patients with reduced ejection fraction.

Background

Heart failure (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 Canadians over 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 has declined, as has the age-standardized all-cause mortality rate among people living with HF. However, Canadians over 40 years of age with HF are six times more likely to die than those without a HF diagnosis. HF with preserved ejection fraction (HFpEF) accounts for at least 50% of the population with HF, and its prevalence is increasing. Evidence shows that the mortality and morbidity of HF with preserved ejection fraction were similar or comparable to those of HF with reduced ejection fraction (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 is significantly affecting their quality of life. The current pharmacological management of HF with reduced ejection fraction include diuretics, beta-blockers, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB), as well as mineralocorticoid receptor antagonist (MRA), sacubitril/valsartan, ivabradine, and dapagliflozin. According to the expert consulted by CADTH, current strategies for the treatment of HF with preserved ejection fraction are limited to supportive therapies focusing on symptom control rather than morbidity or mortality benefit and include ARB, MRA, and sacubitril/valsartan.

Empagliflozin has been approved by Health Canada for for use in adults as an adjunct to standard of care therapy for the treatment of chronic HF. Empagliflozin is a sodium-glucose co-transporter 2 (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 heart failure 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 heart failure.
- A review of 1 sponsor-submitted indirect treatment comparison (ITC) and 1 published ITC retrieved from 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 heart failure.
- 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 clinical expert(s) 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, which is a national charity which through their extensive network, engage patients and their caregivers to provide education, support, and access to treatments and research, provided input for this review. Information for this review was gathered through in-person interviews with 3 patients and 1 caregiver, an on-line survey of 12 respondents held in April 2022, as well as from 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 endpoints for both quantity and quality of life as many patients remain intolerant to beta blockers and in some cases to ACEIs. Respondents expressed a desire to have greater access to proven therapies, improved functional capacity and quality of life as they would like to spend time with loved ones, be able to work on a regular basis, pursue outdoor activities, and be able to travel. There were 16 respondents with experience of using empagliflozin 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), about 33.3% of respondents felt better after taking empagliflozin, while 8.3% reported that they felt worse. Based on the survey results, about 33.3% of respondents described their side effects as manageable, whereas 25% 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 in HFpEF are limited to supportive therapies focusing on symptom control rather than morbidity or mortality benefit, including ARB, MRA, and ARNi, while data with SGLT-2 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, given the ease of use, strength of evidence, safety profile, and familiarity with the use of empagliflozin in patients with type II diabetes mellitus. The population least likely to benefit from empagliflozin treatment are patients with low NT-proBNP levels and those with NYHA classes I and IV due to limited clinical evidence. The clinical experts indicated that the response to therapy in clinical practice is assessed based on the frequency of hospitalizations for HF, 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 heart failure is a major cost burden in the healthcare system. The clinical experts identified the following factors to consider when deciding to discontinue treatment with empagliflozin: 1) the development of severe kidney dysfunction (eGFR < 15 mL/min), and euglycemic diabetic ketoacidosis in patients with diabetes as important adverse events, and 2) 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 trial(s) • Only one other SGLT2 inhibitor dapagliflozin has received HC approval for the treatment of patients with HFrEF. • Dapagliflozin received a positive recommendation in December 2020 for the treatment of HF in patient with NYHA class II or III. Dapagliflozin originally submitted to CADTH for the treatment of HF in patients with NYHA class II, III or IV. • However, the evidence submitted by the sponsor lacked direct comparison with dapagliflozin as a comparator as it includes two placebo-controlled trials: 1. EMPEROR-Reduced which included patients with established HFrEF (LVEF ≤ 40%), with or without T2DM. • EMPEROR-Preserved which included patients with established HFpEF (LVEF > 40%), with or without T2DM	Comment from the drug programs to inform CDEC deliberations.
• In indirect treatment comparison (ITC) demonstrated no statistically significant differences between empagliflozin and dapagliflozin in the composite outcome of time to first event of adjudicated CV death or adjudicated HHF, or for the individual outcomes of time to first adjudicated HHF, time to adjudicated CV death, time to all-cause mortality, or time to worsening renal function. • If the recommendation is to restrict empagliflozin for the treatment of HF in patients with NYHA II or III, which would align with dapagliflozin' s CDEC recommendation, is there evidence support to the use one agent over another? • An exclusion criterion in both trials was "current use or prior use of a SGLT-2 inhibitor". If the recommendation is to list empagliflozin for the treatment of HF in patients with NYHA II, III or IV and a patient progresses to NYHA 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 expert(s) agree with this statement and if so, does empagliflozin fit this unmet need?	No head-to-head trials are available for empagliflozin versus dapagliflozin, but both showed similar benefits in similar populations. There were more similarities than difference 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 with 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 in in HFpEF, this would be an addition to the current therapy, but in HFrEF, this would be an alternative agent to dapagliflozin.

Implementation Issues	Response
Relevant Comparators	
	CDEC acknowledged that the clinical experts noted that there are more studies using SGLT-2 inhibitors in progress and 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, listed as a restricted benefit with criteria for the use in patients with NYHA class II or III as an adjunct to the standard care of therapy in patients with a left ventricular ejection fraction (LVEF) equal or less than 40% • Exceptions include: ○ NIHB, NT, YK, CAF and CSD open benefit ON full benefit with therapeutic notes same as criteria.	Comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
• Based on 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 were receiving both ARNI (sacubitril and valsartan class) and ivabradine (in combination with empagliflozin). However, the clinical experts noted that there is likely more evidence to support a higher number of patients were on sacubitril and valsartan as typically, the use of Ivabradine is only in patients who cannot tolerate Beta blocker or are not achieving hart rate of less than 70 with beta blocker, therefore the extent number of patients on ivabradine would be relatively low number on ivabradine. From the expert's clinical experience, 1-2% of patients were on ivabradine in their practice. Nonetheless, the clinical expert does 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 II diabetes, HF, and a rapid response was just published for CKD. • empagliflozin has received positive CDEC recommendations for Type II diabetes, high risk cardiovascular 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 acknowledge that the availability of empagliflozin may potentially benefit the payers in terms of price negotiations.

CAF = Canadian Armed Forces; CDEC = The Canadian Drug Expert Committee; CKD = chronic kidney disease; CV = cardiovascular; HC = Health Canada; HF = Heart failure; HFrEF = Heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HHF = hospitalization for heart failure; ITC = indirect treatment comparison; LVEF = left ventricular ejection fraction; NIHB = Non-Insured Health Benefits; NT = Northwest Territories; YK = Yukon; NYHA = New York Heart Association; ON = Ontario; SGLT-2I = sodium-glucose co-transposer-2 inhibitor; T2DM = type 2 diabetes mellitus.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

Two phase III, double-blind, placebo-controlled RCTs (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 = 3730) was designed to assess the superiority of empagliflozin at 10 mg compared to matched placebo as an adjunct to standard of care treatment in patient with HF with reduced left ventricular ejection fraction (LVEF ≤ 40%). In EMPEROR-Reduced, patients had a mean age of 66.8 years (SD = 11.0 years), 70.5% were male, and the mean LVEF was 27.5% (SD = 6.0), and most patients (75.1%) had NYHA functional class II. The EMPEROR-Preserved trial (N = 5988) was designed to assess the superiority of empagliflozin at 10 mg compared to matched placebo as an adjunct to standard of care treatment in patient with HF with preserved left ventricular ejection fraction (LVEF > 40%). In EMPEROR-Preserved, patients had a mean age of 71.9 years (SD = 9.4 years), 55.3% were male, and the mean LVEF was 54.3% (SD = 8.8), and most patients (81.5%) had NYHA functional class II.

In both EMPEROR trials, the primary efficacy endpoint was the time to first event of adjudicated CV death or HHF, and the key secondary endpoints were occurrence of adjudicated hospitalization for heart failure (HHF) (first and recurrent), and eGFR (CKD-EPI) cr 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 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) cr 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 the treatment response in patients with HF, while change in eGFR is not commonly used in clinical practice. Other secondary and further endpoints were tested in a non-hierarchical fashion without adjustments for multiplicity.

The time to first event of adjudicated CV death or HHF

In EMPEROR-Reduced, 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 hazard ratio 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 empagliflozin group. Although individual components of the composite primary endpoint were not formally tested for significance, the proportion of HHF was lower in the empagliflozin group (13.2%) compared with placebo (18.3%), while the total proportion of CV deaths was similar across the treatment groups (10.0% vs. 10.8%, respectively).

In EMPEROR-Preserved, 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 hazard ratio 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 HHF was lower in the empagliflozin group (8.6%) relative to placebo (11.8%), while the total proportion of CV deaths was similar across the treatment groups (7.3% vs. 8.2% in the empagliflozin and placebo groups, respectively).

Occurrence of HHF (first and recurrent)

In EMPEROR-Reduced, the total number of HHF (first and recurrent) was lower in patients who received empagliflozin compared to those who received placebo (388 vs. 553, respectively). The hazard rate of recurrent HHF was significantly reduced in the empagliflozin group compared to placebo, with a hazard ratio of 0.70 (95% CI, 0.58 to 0.85; P = 0.0003).

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

eGFR slope of change form baseline

In EMPEROR-Reduced, over the double-blind treatment period, the rate of decline in the eGFR (CKD-EPI) cr 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).

In EMPEROR-Preserved, over the double-blind treatment period, the rate of decline in the eGFR (CKD-EPI) cr per year was slower in the empagliflozin group (–1.25 mL/min/1.73 m^2 per year; 95% CI, –1.47 to –1.04) than in the placebo group (–2.62 mL/min/1.73 m^2 per year; 95% CI, –2.83 to –2.41), 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 HF symptoms

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

KCCQ clinical summary score

In EMPEROR-Reduced, the analysis based on the Randomized set (RS) showed a smaller decline from baseline of –1.30 points (SE = 0.69) in the empagliflozin group than in the placebo group (–3.36 points; SE = 0.69) in the KCCQ clinical summary score at Week 52, with an adjusted mean difference of 2.06 (95% CI, 0.16 to 3.96) favoring 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 score, compared to placebo (35.9%) (OR = 1.23; 95% CI, 1.05 to 1.45).

In EMPEROR-Preserved, the analysis based on the RS showed a slight increase of 0.48 points (SE = 0.47) in the empagliflozin group compared to placebo (–0.92 points; SE = 0.47) in the KCCQ clinical summary score from baseline at Week 52, with an adjusted mean difference of 1.24 (95% CI, 0.05 to 2.44) favoring empagliflozin. Responder analyses showed that at Week 52, 41.7% of patients in the empagliflozin group reported at least a 5-point increase in KCCQ clinical summary score, compared to placebo (38.7%) (OR = 1.12; 95% CI, 0.99 to 1.26).

KCCQ total symptom score

In EMPEROR-Reduced, the analysis based on the RS showed a smaller decline from baseline of a –1.86 points (SE = 0.83) in the empagliflozin group compared to placebo (–4.01 points; SE = 0.86) in the KCCQ total symptom score at Week 52, with an adjusted mean difference of 2.25 (95% CI, 0.20 to 4.30) favoring empagliflozin. Responder analyses showed that at Week 52, 40.4% of patients in the empagliflozin group reported at least a 5-point increase in KCCQ clinical summary score, compared to placebo (38.4%) (OR = 1.12; 95% CI, 0.95 to 1.32).

In EMPEROR-Preserved, the analysis based on the RS showed an increase from baseline of 1.66 points (SE = 0.51) in the empagliflozin group compared to placebo (–0.51 points; SE = 0.52) in the KCCQ total symptom score at Week 52, with an adjusted mean difference of 1.77 (95% CI, 0.48 to 3.06) favoring empagliflozin. Responder analyses showed that at Week 52, 43.2% of patients in the empagliflozin group reported at least a 5-point increase in KCCQ total symptom score, compared to placebo (38.1%) (OR = 1.20; 95% CI, 1.06 to 1.35).

Harms Results

Adverse events

In EMPEROR-Reduced, 1420 (76.2%) patients in the empagliflozin group and 1463 (78.5%) patients in the placebo group experienced at least 1 AE. Patients in the empagliflozin and placebo groups experienced TEAEs in a similar frequency (15.2% and 12.2%, respectively). The most common TEAEs occurring in at least 0.5% of patients in the empagliflozin or placebo groups were

hypotension (2.3% vs. 1.8%, respectively), renal impairment (1.4% and 1.1%, respectively), urinary tract infection (1.4% in each group), and hypoglycaemia (0.9% and 1.1%, respectively).

In EMPEROR-Preserved, 2574 (85.9%) patients in the empagliflozin group and 2585 (86.5%) patients in the placebo group experienced at least 1 AE. Patients in the empagliflozin and placebo groups experienced TEAEs in a similar frequency (16.5% and 13.8%, respectively). The most common TEAEs occurring in at least 0.5% of patients in the empagliflozin or placebo groups were urinary tract infection (3.1% vs. 2.4%, respectively), hypotension (1.6% and 1.1%, respectively), renal impairment (1.3% and 1.2%, respectively), and hypoglycaemia (1.0% in each group).

In EMPEROR-Reduced, 772 (41.4%) patients in the empagliflozin group and 896 (48.1%) patients in the placebo group experienced ≥ 1% SAEs. In EMPEROR-Preserved, 1436 (47.9%) patients in the empagliflozin group and 1543 (51.6%) patients in the placebo group experienced ≥ 1% SAEs.

Withdrawals due to adverse events

In EMPEROR-Reduced, 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 EMPEROR-Reduced, and 19.1% and 18.4% in EMPEROR-Preserved, respectively). The most frequently reported types of WDAEs in both trials were cardiac failure, death, acute myocardial infarction, renal impairment, and urinary tract infection.

Mortality

In both EMPEROR trials, the proportion of fatal AEs during the double-blind treatment phase was similar across the treatment groups (9.7%). In EMPEROR-Preserved, 9.9% of AEs in the empagliflozin group and 9.9% in the placebo groups resulted in death.

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 (9.4% vs. 10.3%, and 12.1% vs. 12.8% in the empagliflozin and placebo groups in EMPEROR-Reduced and EMPEROR-Preserved, respectively), followed by hypotension (9.4% vs. 8.7%, and 10.4% vs. 8.6% in the empagliflozin and placebo groups in EMPEROR-Reduced and EMPEROR-Preserved, respectively), urinary tract infection (4.9% vs. 4.5%, and 2.4 vs. 2.3% in the empagliflozin and placebo groups in EMPEROR-Reduced and EMPEROR-Preserved, respectively), and bone fracture (2.4% vs. 2.3%, and 4.5% vs. 4.2% in the empagliflozin and placebo groups in EMPEROR-Reduced and EMPEROR-Preserved, respectively). No new safety concerns were identified.

Critical Appraisal

Internal validity

Both EMPEROR-Reduced and EMPEROR-Preserved trials appeared to have accepted 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 as high concentrations of NT-proBNP can confirm HF in patients who present with dyspnea, when the clinical diagnosis remains uncertain.[2] However, the clinical experts consulted by CADTH highlighted that physicians only need to perform NT-proBNP tests in 10-20% 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 EMPEROR-Reduced and EMPEROR-Preserved, respectively, including fatal events), while 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 the HF more than intolerance to the drug under review. An independent clinical expert blinded 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. While improvement in health-related quality of life (HRQoL), HF symptoms, and functional ability were of primary importance of patients with HF according to 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 KCCQ and EQ-5D-5L instruments. Clinical experts indicated that these tools are not used in clinical practice, but are used in multiple studies, allowing comparisons between different treatments. Since 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, there is a high risk of bias as patients who completed the questionnaires may be fundamentally different than those who did not complete (i.e., differences in treatment response, AEs, etc.). Assessment of functional ability was based on the change in NYHA functional class from baseline at Week 52 using descriptive statistics. 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 against other comparators, including dapagliflozin, or sacubitril/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 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. While empagliflozin has been approved by Health Canada for use as an adjunct to standard of care therapy in patients with chronic HF regardless of NYHA class, CADTH was unable to draw conclusions related to patients with NYHA functional classes I and IV, since both trials excluded patients who had NYHA class I, and there was a very small proportion of patients who had NYHA class IV. One of the clinical experts consulted highlighted that the benefit of empagliflozin in patients with NYHA class IV is unclear due to limited clinical data and high mortality, while another clinical expert indicated that he would prescribe empagliflozin to patients with NYHA class IV. In addition, clinical experts indicated that they would not prescribe empagliflozin to patients with chronic HF with NYHA classes I, as they are asymptomatic, which is consistent with the reimbursement request. About 48% of patients in both trials were screening failures, most commonly because of NT-proBNP levels being 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 as 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 and could benefit more from treatment with empagliflozin than the population in the real-world setting. In the EMPEROR-Preserved trial, about 33% of patients had mid-range LVEF (41 to 49%); however, clinical experts do not expect this to be a major issue with the generalizability of the trial results, as 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 patients included in both EMPEROR trials were younger, as the median age of population with HF in the 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%) which were enrolled, as 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; and thus, they represented patients who were optimally managed, while the clinical experts noted that a goal directed treatment of HF is suboptimal in clinical settings. Lastly, although the recommended dosage of empagliflozin for the treatment of HF is 10 mg, clinical experts indicated that both dosages 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 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 HFrEF. The sponsor chose to restrict the ITC to the two pivotal phase 3 trials for each drug. These represented the studies that were submitted for the purposes of regulatory approval, as well as being the two studies with the largest sample size for each drug, the EMPEROR-Reduced and DAPA-HF trials. Both EMPEROR-Reduced and DAPA-HF were phase 3, double blind, multi-centre studies comparing SOC to either empagliflozin or dapagliflozin, respectively. The mean duration of follow-up was slightly

longer in DAPA-HF (18.2 months), compared to EMPEROR-Reduced (16 months). The inclusion criteria were similar with the exception of EMPEROR-Reduced, which allowed for higher baseline NT-proBNP and higher eGFR filtration rate, according to the study inclusion criteria. The primary endpoint in EMPEROR-Reduced was time-to-first hospitalization for heart failure or CV death, whereas in DAPA-HF, this composite endpoint also included urgent heart failure visits. For the purposes of the analysis, these endpoints were considered equivalent. Both studies were assessed by the sponsor, according to the standard NICE risk of bias checklist, to have low risk of bias.

Efficacy Results

The Bucher ITC compared empagliflozin against dapagliflozin in patients with HFrEF in time to first event of adjudicated CV death or adjudicated HHF, time to first adjudicated HHF, time to adjudicated CV death, time to all-cause mortality, and time to worsening renal function. There were no endpoints that resulted in a HR excluding 1 for the comparison of empagliflozin versus dapagliflozin. The primary endpoint from both studies, time to first event of adjudicated CV death or adjudicated HHF, showed no difference between empagliflozin and dapagliflozin with a HR (95% CI) of 1.00 (0.82 to 1.21).

Critical Appraisal

The sponsor conducted a Bucher ITC comparing empagliflozin against 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 to be 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, estimating 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 included a broader primary composite endpoint in DAPA-HF (the impact of which is uncertain), baseline characteristics indicating sicker patients in EMPEROR-Reduced potentially biasing results in favour of empagliflozin, and a more effective basket of background SOC therapies used in EMPEROR-Reduced potentially biasing results against empagliflozin. Despite the described differences between the 2 studies, there does not appear to be evidence for a difference in treatment effects between empagliflozin and dapagliflozin, aligning with the opinion of clinical experts consulted. 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 indicating no difference between empagliflozin and dapagliflozin were consistent with the sponsor submitted ITC and the 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 as other relevant studies for this report: EMPERIAL-Reduced and EMPERIAL-Preserved trials. The CADTH review team identified two phase III, multicenter, 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 one of the outcomes of interest, Kansas City Cardiomyopathy Questionnaire (KCCQ), was considered exploratory as the primary endpoint was not met in the two trials. Therefore, though 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 and safety.

Description of studies

EMPERIAL-Reduced

The effect of empagliflozin on exercise ability and hf symptoms in patients with chronic heart failure with reduced ejection fraction (EMPERIAL-Reduced) trial was a phase III, multicenter, randomized, double-blind, placebo-controlled study trial that aimed to evaluate the effect of empagliflozin (10 mg once daily) on exercise capacity and patient-reported outcomes as compared to placebo in patients with heart failure (HF) with reduced ejection fraction (HFrEF) (defined as LVEF $\leq$ 40%), with or without type 2 diabetes mellitus (T2DM). A total of 312 patients were enrolled across 109 sites from 8 countries in Australia, Canada, Germany, Greece, Italy, Norway, Poland, Portugal, Spain, Sweden, and the US. 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 (standard deviation [SD] = 10.2 years), the majority of patients were male (74.4%) and White (84.3%). The

cause of HF was ischaemic 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

The effect of empagliflozin on exercise ability and hf symptoms in patients with chronic heart failure with preserved ejection fraction (EMPERIAL-Preserved) trial was a phase III, multicenter, randomized, double-blind, placebo-controlled study trial that aimed to evaluate the effect of empagliflozin (10 mg once daily) on exercise capacity and patient-reported outcomes as compared to placebo in patients with HF with preserved ejection fraction (HFpEF) (defined as LVEF > 40%), with or without T2DM. A total of 315 patients were enrolled across 108 sites from 8 countries in Australia, Canada, Germany, Greece, Italy, Norway, Poland, Portugal, Spain, Sweden, and the US. 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), the majority of patients were male (56.8%) and White (87.3%). The cause of HF was ischaemic 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 endpoint was change from baseline in 6-minute walk test distance (6MWTD) at Week 12. Key secondary endpoints were change from baseline in KCCQ- Total Symptom Score (KCCQ-tss), and Chronic Heart Failure Questionnaire Self-administered Standardized format (CHQ-SAS) dyspnoea score at Week 12. Results for KCCQ-tss and CHQ-SAS dyspnoea score are presented in accordance with the protocol for the CADTH review. The median difference from baseline to Week 12, empagliflozin vs. placebo, in KCCQ-TSS was 3.13 (95% CI, 0.00 to 7.29) and 2.08 (95% CI, –2.08 to 6.25) in EMPERIAL-Reduced and EMPERIAL-Preserved, respectively. The median difference, empagliflozin vs. placebo, in CHQ-SAS dyspnoea score was 0.10 (95% CI, –0.20 to 0.40) and –0.07 (95% CI, –0.35 to 0.20) in EMPERIAL-Reduced and EMPERIAL-Preserved, respectively. The results for other symptom outcomes are presented in the Other Relevant Evidence section.

Harms Results

There was no notable difference for empagliflozin versus placebo regarding the overall frequencies of any adverse event (AE) or any AE leading to treatment discontinuation in both trials. Serious AEs (SAEs) were less frequently reported with empagliflozin than placebo in EMPERIAL-Reduced (empagliflozin 12.7% vs. placebo 18.4%) and EMPERIAL-Preserved (empagliflozin 13.5% vs. placebo 17.3%). Decreased kidney function was reported with similar frequencies in both groups. No ketoacidosis or confirmed hypoglycaemic events occurred in participants without type 2 diabetes. No new safety concerns were identified.

Critical Appraisal

The following limitations were identified: HF is a chronic condition, which means 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 EMPERIAL-Reduced and EMPERIAL-Preserved trials is 12 weeks, which may not be sufficient to assess meaningful changes in the outcome measures. In addition, the EMPERIAL trials were powered to detect a 30 m 6MWTD improvement, the study sample size may not be sufficient enough to detect any between group changes that were less than 30 m. In addition, as the primary endpoint, change from baseline in 6MWTD at Week 12, was not met, the analyses of all secondary outcomes, such as KCCQ-tss and CHQ-SAS dyspnoea score, were considered exploratory. While the changes in KCCQ-tss and CHQ-SAS dyspnoea 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 6MWTD) 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 study 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 standard of care 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 hospitalization for HF, as well as occurrence of adjudicated first and recurrent hospitalization for HF. The annual rate of decline in the estimated glomerular filtration rate 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 health-related quality of life, 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 against other relevant comparators, including dapagliflozin, sacubitril/valsartan, and ivabradine in the HFrEF population, were available for this review. The median duration of EMPEROR-Reduced and EMPEROR-Preserved was 1.31 years and 2.15 years, respectively. Thus, long-term efficacy and safety in patients with chronic HF is uncertain. While empagliflozin has been approved by Health Canada for use as an adjunct to standard of care therapy in patients with chronic HF regardless of NYHA class, CADTH was unable to draw conclusions related to patients with NYHA functional classes I and IV, since both pivotal trials excluded patients who had NYHA class I, and there was a very small proportion of patients who had NYHA class IV. No new safety signals were identified in patients with HF with reduced and preserved ejection fractions. The sponsor-submitted ITC, despite limitations, suggested that there is no difference between empagliflozin and dapagliflozin in the HFrEF population, which was consistent with the opinion of clinical experts consulted.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	Patients with reduced or preserved ejection fraction heart failure, aligned with the population of the EMPEROR-Reduced and EMPEROR-Preserved trials: • Heart failure with reduced ejection fraction (HFrEF): adults with chronic heart failure (functional class II, III, or IV) with left ventricular ejection fraction (LVEF) ≤ 40% • Heart failure with preserved ejection fraction (HFpEF): adults with diagnosed symptomatic chronic heart failure (NYHA functional class II, III, or IV) with a LVEF > 40%
Treatments	Empagliflozin (EMPA) + standard of care (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	Empagliflozin, 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: dapagliflozin (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 versus DAPA+SoC in the HFrEF population were derived from a sponsor-submitted indirect treatment comparison (ITC)
Key limitations	• The full Health Canada population was not captured in the clinical trials, as patients 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, divided into quartiles, does not adequately reflect heart failure in clinical practice and do not represent homogenous heart failure health states. This modelling approach prevented CADTH from fully validating the sponsor's model, and, where 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/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 no difference between EMPA+SoC and DAPA+SoC for cardiovascular and all-cause mortality, hospitalizations due to heart failure, and a composite renal outcome. 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.

Component	Description
	• 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 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 subgroup. CADTH was unable to address the remaining limitations noted above. 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 to SoC (incremental costs: $539; incremental QALYs: 0.11). When compared to 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 decisions maker's WTP threshold was above $11,081 per QALY. ○ In the NYHA III/IV subgroup, EMPA+SoC was associated with an ICER of $8,883 per QALY compared to 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 above $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 to 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/IV subgroup, EMPA+SoC was associated with lower QALYs (incremental QALYs: –0.23) and higher costs (incremental costs: $540) when compared to SoC (dominated).

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 (EMPA), as patients with NYHA class I heart failure 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 heart failure patients with concurrent type 2 diabetes mellitus (T2DM) who are currently prescribed an SGLT2i as part of their diabetes management.
- Uptake of EMPA 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 formulary list prices for some jurisdictions.

CADTH reanalyses assumed that not all T2DM patients currently receive an SGLT2i, adopted a higher uptake of EMPA in the HFpEF population, and corrected the price of DAPA. CADTH reanalyses suggest that the overall budget impact to the public drug plans of introducing EMPA for the treatment of heart failure is $170,069,261 over three 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 EMPA and the proportion of patients currently receiving an SGLT2i for the treatment of T2DM. Should patients with NYHA class I be prescribed EMPA, the budget impact of reimbursing EMPA will be higher than the CADTH base case.

Canadian Drug Expert Committee (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 of expert committee members did not attend

Conflicts of Interest: None