CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

DAPAGLIFLOZIN (FORXIGA — AstraZeneca Canada Inc.)
Indication: in adults, as an adjunct to standard of care therapy, for the treatment of heart failure with reduced ejection fraction (HFrEF) to reduce the risk of cardiovascular death, hospitalization for heart failure (HF) and urgent HF visit.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that dapagliflozin (Forxiga) should be reimbursed as an adjunct to standard of care therapy, for the treatment of HFrEF only if the following condition is met.

Conditions for Reimbursement

Initiation criteria

Reimburse as an adjunct to standard of care therapy only in adults with New York Heart Association class II and III heart failure. Standard of care therapies include beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, plus a mineralocorticoid receptor antagonist.

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that dapagliflozin (Forxiga) should be reimbursed as an adjunct to standard of care therapy, for the treatment of HFrEF only if the following condition is met.

Condition for Reimbursement

Initiation criterion

Reimburse as an adjunct to standard of care therapy only in adults with New York Heart Association (NYHA) class II and III heart failure. Standard of care therapies include beta-blockers, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), plus a mineralocorticoid receptor antagonist.

Reasons for the Recommendation

1. In the pivotal trial (DAPA-HF), 16.3% of patients in the dapagliflozin group and 21.2% of patients in the placebo group reported a composite primary outcome event of CV death, HF hospitalization or urgent HF visit. The time to occurrence of the composite of primary events was greater for the dapagliflozin-treated patients (hazard ratio (HR) 0.74, 95% confidence interval (CI), 0.65 to 0.85, P < 0.0001) relative to placebo. Similar treatment effects were noted for the analysis of time to first occurrence of CV death or HF hospitalization (HR 0.75 95% CI, 0.65 to 0.85, P < 0.0001). For each component of the primary outcome, the time to first event was greater for dapagliflozin-treated patients. The total number of CV deaths or HF hospitalizations was lower in the dapagliflozin versus placebo groups (average 16.3 events per 100 person years [PYs] versus 21.6 events per 100 PYs, respectively) with a rate ratio of 0.75 (95% CI, 0.65 to 0.88, P = 0.0002).

2. At the sponsor-submitted price, in patients with HF in NYHA class II, dapagliflozin is associated with an incremental cost-effectiveness ratio (ICER) of $8,760 per quality-adjusted life-year (QALY) compared to standard of care. For patients in class III or IV, dapagliflozin was dominated by standard of care; that is dapagliflozin was more costly and was associated with fewer QALYs; however, this was associated with a high degree of uncertainty about the clinical efficacy of dapagliflozin in patients with NHYA class III and IV HF.

Discussion Points

- According to the clinical experts consulted for this review, the between-group differences in CV death and HF hospitalizations were clinically important, particularly considering that patients were already receiving guideline-recommended treatment for HF.
- The DAPA-HF trial population does not reflect the ethnic diversity of Canada and excluded patients with more advanced disease including those with recent HF hospitalization or CV events, and those with poor or worsening renal function. Most patients were NYHA class II (68%) and less than 1% had NYHA class IV HF.
- The DAPA-HF trial was not designed to test for superiority of dapagliflozin for health-related quality of life, which was of primary importance to patients. The EQ-5D results reported had limitations due to missing data [redacted] and this outcome was not part of the statistical testing hierarchy. The DAPA-HF study found statistically significant differences favouring dapagliflozin for the change from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (rank analysis of covariance [ANCOVA] P <0.0001); however, the clinical relevance of these results is difficult to assess.

- Data are lacking comparing dapagliflozin to other second-line treatments for HFrEF, such as sacubitril/valsartan or ivabradine. The sponsor supplied a matching-adjusted indirect comparison (MAIC) that evaluated the efficacy and safety of dapagliflozin compared to sacubitril/valsartan as add-on to standard therapies in adults with HFrEF. However, the analysis had several limitations that threatened the internal validity of the results. Most notable were differences in the study design and populations enrolled in the two trials (such as the enrolment of an enriched population in the PARADIGM-HF study), and the derivation of patient weights independently for the active and control groups of the DAPA-HF study. The methods used to conduct the MAIC were not consistent with National Institute for Health and Care Excellence technical guidance and are of uncertain validity. As a result, no conclusions can be drawn from the indirect comparison.

Background

Dapagliflozin has a Health Canada indication in adults, as an adjunct to standard of care therapy, for the treatment of HFrEF to reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visit. Dapagliflozin belongs to the sodium-glucose cotransporter-2 (SGLT2) inhibitor drug class. It is available as 5 mg and 10 mg oral tablets. The recommended dose for patients with HFrEF is 10 mg once daily, in conjunction with other HF therapies.

Submission History

Dapagliflozin and dapagliflozin/metformin fixed-dose combination tablets were previously reviewed in 2015 and 2016 and were recommended for reimbursement in patients with type 2 diabetes to improve glycemic control (see Notice of CDEC Final Recommendation November 20, 2015 and July 20, 2016). Dapagliflozin received a do not list recommendation for the treatment of type 2 diabetes when used in combination with metformin and a sulfonylurea (see Notice of CDEC Final Recommendation, April 27, 2016).

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: a systematic review of randomized controlled trials of dapagliflozin and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience in treating patients with HF, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Three responses to CADTH's call for patient input were received for the review of dapagliflozin. The patient groups included the HeartLife Foundation, the Cardiac Health Foundation of Canada, and the Heart Failure support group of Manitoba. Patient perspectives were obtained from in-person meetings and workshops, patient interviews, and an online survey. The following is a summary of key input from the perspective of the patient groups:

- People with HF experience a wide range of physical, social, and emotional challenges that have a dramatic effect on their lives and the lives of their family caregivers.
- Although a number of treatments are available for HF, the condition requires daily monitoring, adherence, and vigilance on the part of the patient to control the delicate balance of symptoms.
- Patients hope that treatments for HF will reduce their symptoms, improve their quality of life (i.e., breathe easier, walk longer, continue to work, and participate in other activities), prevent hospitalizations, reduce mortality, and have fewer adverse effects or at least more tolerable adverse effects.

Clinical Trials

The systematic review included two double-blind randomized placebo-controlled trials of patients with HFrEF.

The DAPA-HF study (N = 4,744) evaluated the efficacy of dapagliflozin 10 mg daily versus placebo as add-on to standard of care therapy in adults with HFrEF (LVEF ≤ 40%; NYHA function class II to IV). The median follow-up duration of this event driven trial was 18.2 months, with > 99% of patients completing the study.

The 12-week DEFINE-HF study (N = 263) evaluated the effect of dapagliflozin in patients with HFrEF (LVEF ≤ 40%). Patients were randomized to dapagliflozin 10 mg daily or placebo as add-on to standard of care HF therapy.

There was no direct evidence comparing dapagliflozin to other add-on therapies such as sacubitril/valsartan or ivabradine.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed the following: time to first occurrence of CV death, hospitalization for HF, or an urgent HF visit; all-cause mortality; change from baseline in HF symptoms; and health-related quality of life.

The primary outcome in the DAPA-HF study was the time to first occurrence of CV death, hospitalization for HF, or an urgent HF visit. In the DEFINE-HF study, the co-primary outcomes included biomarker and health status measures that were not outcomes of interest according to the CADTH review protocol.

- The change in HF symptoms was measured using the KCCQ total symptom score. The KCCQ symptom domain assesses the symptom burden and frequency of fatigue, shortness of breath, paroxysmal nocturnal dyspnea, and edema or swelling, each measured on a Likert scale. Symptom burden and frequency are combined into the total symptom score which has a range of 0 to 100, with higher scores representing better outcomes. There is evidence to support the validity, reliability and responsiveness of the KCCQ and a minimum important difference (MID) of 4.7 to 5.0 points has been reported for the total symptom score.
- Health-related quality of life was measured using the European Quality of Life 5-dimension 5-level (EQ-5D-5L). The instrument includes five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, that are each rated on five levels of perceived problems measured on that day. The value set for the EQ-5D-5L from UK was used to convert the descriptive system to the health status index score (range -0.594 to 1), which was anchored at zero (health state value equal to dead) and one (full health). A Canadian-specific MID of 0.037 has been reported, but no MID in patients with HF was found.

Efficacy

During the DAPA-HF study, 16.3% of patients in the dapagliflozin group and 21.2% of patients in the placebo group reported a primary outcome event of CV death, HF hospitalization, or urgent HF visit. The time to first occurrence of CV death, hospitalization for HF, or an urgent HF visit was increased for patients in the dapagliflozin group versus placebo based on a HR of 0.74, 95% confidence interval (CI), 0.65 to 0.85, P < 0.0001. Similar treatment effects were noted for the analysis of time to first occurrence of CV death or HF hospitalization (HR 0.75 05% CI, 0.65 to 0.85, P < 0.0001).

In the dapagliflozin group, 11.6% of patients died from any cause, compared with 13.9% of patients in the placebo group, with an event rate of 7.9 deaths/100 PY versus 9.5 deaths/100 PY, respectively. The time-to-event analysis reported a HR of 0.83 (95% CI, 0.71 to 0.97), but due to failure of a prior outcome in the statistical hierarchy, statistical testing of this outcome was not conducted.

The DAPA-HF study found statistically significant differences favouring dapagliflozin for the change from baseline in the KCCQ total symptom score (rank analysis of covariance [ANCOVA] P < 0.0001). No statistically significant difference between groups was detected in health-related quality of life outcomes based on exploratory EQ-5D-5L data.

Harms (Safety)

- During the DAPA-HF study, which had an 18-month median follow-up duration, 36% and 40% of patients in dapagliflozin and placebo groups, respectively, experienced a serious adverse event. Five percent of patients in each group stopped treatment due to adverse events. The frequency of renal adverse events (6.0% and 6.7%) and volume depletion events (7.2% and 6.5%) were similar in dapagliflozin and placebo groups, respectively. Three patients in the dapagliflozin group experienced diabetic ketoacidosis (adjudicated event), all of which were serious adverse events: one patient died. Four patients per group experienced a major hypoglycemic event; all of whom had diabetes at baseline.
- The DAPA-HF study did not collect data on all adverse effects, thus it is unclear if the overall pattern of adverse effects is similar in patients who experienced HF, as was observed in the previously published dapagliflozin trials in patients with diabetes.

- In the DEFINE-HF study, 23% and 18% of patients in the dapagliflozin and placebo groups, respectively, reported a serious adverse event over the 12-week treatment period, with 8% and 9% of patients stopping study drug due to adverse events. One patient in the dapagliflozin group died due to worsening HF, and one sudden cardiac death was reported in the placebo group.

Indirect Treatment Comparisons

The sponsor supplied a MAIC that evaluated the efficacy and safety of dapagliflozin compared to sacubitril/valsartan as add-on to standard therapies in adults with HFrEF. The methods used to conduct the MAIC were not consistent with National Institute for Health and Care Excellence technical guidance and the analysis had several limitations that threatened the internal validity of the results. Some of the key limitations included clinical heterogeneity between the trials, use of data driven approach to identify potential effect modifiers, and independent derivation of patient weights for each treatment group in the DAPA-HF study. Due to the limitations of the analysis, no conclusions could be drawn from the MAIC.

Cost and Cost-Effectiveness

Dapagliflozin is available as a 5 mg and 10 mg tablets. At a recommended dose of 10 mg daily, at the submitted price of $2.73 per 10 mg tablet, the annual per patient cost is $996. Dapagliflozin is given in combination with standard therapy (ST), which consists of ACEis (or ARBs), beta-blockers, and mineralocorticoids/aldosterone antagonists.

The sponsor submitted a cost-utility analysis based on a Markov model and compared dapagliflozin plus (DAPA+ST) to ST alone as well as sacubitril/valsartan+ST as a scenario analysis. The analysis was conducted from a public health care payer perspective, over a patient lifetime time horizon (approximately 35 years) with a monthly cycle length. The model comprised 17 health states relating to the patient's NYHA class (I, II, III, and IV), whether they had type 2 diabetes mellitus (T2DM) and whether they were still on DAPA+ST treatment. In addition to the transitions between health states, the model provides estimates of the proportion of the cohort who experience the following three events each cycle: hospitalization for HF, urgent HF visit, and death. The likelihood of each event occurring is influenced by NYHA class, whether the patient is on DAPA+ST, and whether the patient has T2DM. The following adverse events associated with treatment were included: volume depletion, renal events, hypoglycemic events, fractures, diabetic ketoacidosis, and amputation. The majority of model inputs were derived from the DAPA-HF clinical trial.

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

- The economic submission (both the model and report) lacked transparency and flexibility. CADTH identified errors in the submitted model that required correcting by the sponsor and is concerned that there may still be outstanding issues that have not been identified given the complexity of the model approach. Despite a request from CADTH, this limitation with model presentation was not addressed by the sponsor.
- Based on CADTH guidance from clinical experts for target populations, analysis stratified by NYHA class should be the primary analysis (NYHA II, III, and IV). Analyses by NYHA class were not conducted by the sponsor.
- The sponsor stated in the submitted report that [redacted].
- The model predicted a high proportion of patient's NYHA status would improve, which is contrary to what is known about HF.
- Both HF hospitalizations and the costs of cardiovascular deaths (which would cover hospitalization costs) are included in the model, likely resulting in double counting of hospital costs.
- The CADTH Clinical Review states that no conclusions can be drawn from the MAIC of DAPA+ST versus sacubitril/valsartan+ST. Thus, no comparison in terms of cost-effectiveness can be made.

CADTH was able to account for some of the identified limitations: [redacted] providing a stratified analysis by NYHA class, removing ability for NYHA to improve, and removing CV mortality costs to prevent double counting. CADTH found that for patients in NYHA class II, the ICER for DAPA+ST versus ST alone was $8,760 per QALY. For patients in NYHA class III and IV, DAPA+ST was dominated by ST, meaning that DAPA+ST was more costly and associated

with fewer QALYs than ST. This suggests that dapagliflozin is likely cost-effective for the treatment of patients in NYHA II class, but not cost-effective in NYHA class III and IV. Given [redacted] in the DAPA-HF trial, an ICER below $50,000 per QALY for DAPA+ST versus ST could not be achieved with any level of price reduction for DAPA.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 18, 2020 Meeting

Regrets

None

Conflicts of Interest

None