



CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

EMPAGLIFLOZIN

(Jardiance — Boehringer Ingelheim [Canada] Ltd.)

Indication: Prevention of Cardiovascular Mortality in Type 2 Diabetes Mellitus

Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that empagliflozin be reimbursed as an adjunct to diet, exercise, and standard care therapy to reduce the incidence of cardiovascular (CV) death in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease who have inadequate glycemic control, if the following criteria are met:

Criteria:

- Patients have inadequate glycemic control despite an adequate trial of metformin.
- Patients have established cardiovascular disease as defined in the EMPA-REG OUTCOME trial.

Reasons for the Recommendation:

1. In the EMPA-REG OUTCOME trial, empagliflozin 10 mg and 25 mg appeared to be safe and reduced CV mortality when used adjunctively with standard antidiabetic medications in patients with T2DM who are at high risk for CV disease when compared with placebo. The impact of empagliflozin on myocardial infarction (MI), stroke, hospitalization for heart failure, renal or other microvascular outcomes is unclear given the limitations of the EMPA-REG OUTCOME trial.
2. The manufacturer-submitted economic model indicated a high probability of empagliflozin being cost-effective, and limitations to the model were unlikely to significantly change the estimated incremental cost-utility ratio.

Of Note:

- When evaluating the costs of empagliflozin to drug plans, jurisdictions should consider the potential impact on health system sustainability if all patients who have T2DM and a history of CV disease were to be treated with this drug.
- Established CV disease defined as one of the following:
 - history of MI
 - multi-vessel coronary artery disease in two or more major coronary arteries (irrespective of revascularization status)

- single-vessel coronary artery disease with significant stenosis and either a positive non-invasive stress test or discharged from hospital with a documented diagnosis of unstable angina within 12 months prior to selection
- last episode of unstable angina > 2 months prior with confirmed evidence of coronary multi-vessel or single-vessel disease
- history of ischemic or hemorrhagic stroke
- occlusive peripheral artery disease.

Other Discussion Points:

- CDEC acknowledged the EMPA-REG OUTCOME trial had significant methodological limitations. These limitations included deviation from standard outcome definitions, multiple protocol amendments before and after the interim analysis, questions regarding the reliability of outcome ascertainment, and lack of control for type 1 error. This trial was designed predominately as a safety trial, not as an efficacy trial, and in light of this CDEC recognizes that there is a further need for evidence development to confirm the results of this trial.
- While the trial achieved a statistically significant reduction in the primary composite outcome, several secondary outcomes did not achieve statistical significance in exploratory analysis, including MI, non-fatal MI, silent MI, stroke, non-fatal stroke, transient ischemic attack, coronary revascularization procedures, and hospitalization for unstable angina. There was a statistically significant reduction in hospitalization for heart failure; however, these results are uncertain given the exploratory nature of the analysis, a trial-specific definition of heart failure hospitalization, and multiple protocol amendments to the definition of heart failure hospitalization during the course of the trial.
- CDEC noted the patient population had a significant history of CV disease, with 76% of patients reporting a history of coronary artery disease and 23% reporting a history of stroke. CDEC also noted that the majority of patients had T2DM for more than 10 years, and most patients were on two or more antidiabetic drugs at baseline.

Background:

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT-2) inhibitor that received Health Canada approval as an adjunct to diet, exercise, and standard care therapy to reduce the incidence of CV death in patients with T2DM and established CV disease who have inadequate glycemic control.

Empagliflozin is available in 10 mg and 25 mg tablets. The recommended starting dose is 10 mg once daily; in patients who can tolerate 10 mg once daily and require additional glycemic control, the dose can be increased to 25 mg once daily.

Summary of CDEC Considerations

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of empagliflozin and a critique of the manufacturer's pharmacoeconomic evaluation and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The Canadian Diabetes Association responded to the CDR call for patient input. Surveys were used to collect perspectives of patients with T2DM. CDEC heard the following:

- Poorly controlled T2DM can result in serious long-term complications such as blindness, heart disease, kidney problems, nerve damage, and erectile dysfunction.
- Diabetes, and the related stigma, is associated with a psychological and emotional burden for patients.
- Those with T2DM hoped to have blood glucose levels under control, avoid hypoglycemia, and avoid long-term complications. Additionally, many respondents also hope to reduce the number of drugs taken, as well as insulin injections.

Clinical Trials

The systematic review included one double-blind, event-driven, RCT (EMPA-REG OUTCOME N = 7,020), which was designed to assess the CV safety (non-inferiority) of empagliflozin 10 mg and 25 mg daily versus placebo (as add-on therapy to standard care), in patients with T2DM and high CV disease risk. In this event-driven trial, patients were followed until a minimum of 691 primary composite outcome events were reported (median follow-up 3.1 years). Also of note, the primary outcome in the study does not address the manufacturer's reimbursement request.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- time to first occurrence of CV death, non-fatal MI (excluding silent MI), or non-fatal stroke
- time to first occurrence of CV death, non-fatal MI (excluding silent MI), non-fatal stroke, or hospitalization for unstable angina
- time to CV mortality
- time to all-cause mortality
- time to heart failure hospitalization.

The primary outcome was the time to first occurrence of CV death, non-fatal MI, or non-fatal stroke for the pooled empagliflozin groups versus placebo.

Efficacy

- Fewer patients in the pooled empagliflozin group experienced a major CV adverse event (first occurrence of CV death, non-fatal MI, or non-fatal stroke), than in the placebo group (10.5% versus 12.1%, respectively) (adjusted hazard ratio [adj HR] 0.86 95% confidence interval [CI], 0.74 to 0.99). Empagliflozin was non-inferior to placebo, based on the non-inferiority margin of 1.3 ($P < 0.0001$), and also showed superiority versus placebo ($p = 0.019$ 1-sided).
- Empagliflozin was non-inferior to placebo based on the time to first occurrence of CV mortality, MI, stroke, or hospitalization for unstable angina, (adj HR 0.89; 95% CI, 0.78 to 1.01). Superiority was not achieved.

- Fewer patients in the empagliflozin group died due to CV causes than in the placebo group (3.7% versus 5.9%) (adj HR 0.62; 95% CI, 0.49 to 0.77). The exploratory analysis of all-cause mortality showed similar results (adj HR 0.68; 95% CI, 0.57 to 0.82).
- Exploratory analysis of time to hospitalization for heart failure favoured the empagliflozin group compared with placebo (2.7% versus 4.1%, adj HR 0.65; 95% CI, 0.50 to 0.85).
- Exploratory analysis for other secondary outcomes failed to achieve statistical significance, including MI [adj. HR (95% CI) 0.87 (0.70 to 1.09)], non-fatal MI [adj. HR (95% CI) 0.87 (0.70 to 1.09)], silent MI [adj. HR (95% CI) 1.28 (0.70, 2.33)], stroke [adj. HR (95% CI) 1.18 (0.89 to 1.56)], non-fatal stroke [adj. HR (95% CI) 1.24 (0.92 to 1.67)], transient ischemic attack [adj. HR (95% CI) 0.85 (0.51 to 1.42)], coronary revascularization procedures [adj. HR (95% CI) 0.86 (0.72 to 1.04)], and hospitalization for unstable angina [adj. HR (95% CI) 0.99 (0.74 to 1.34)].

Harms (Safety and Tolerability)

- The adverse events reported in the three-year EMPA-REG study were similar to those identified in previous empagliflozin clinical trials.
- Serious adverse events were reported in 37% and 39% of patients in the empagliflozin 10 mg and 25 mg groups, respectively, and 42% of patients in placebo.
- The percentage of patients who stopped treatment due to adverse events was similar in the placebo group (19%) and the empagliflozin groups (18% and 17% with 10 mg and 25 mg, respectively).
- Genital infections were reported more frequently in the empagliflozin groups (6%) compared with placebo (2%), and were more common in women than men.

Cost and Cost-Effectiveness

The manufacturer submitted a price of \$2.6177 per 10 mg or 25 mg tablet of empagliflozin (\$2.62 daily, regardless of dose).

An economic evaluation was provided by the manufacturer to determine the cost-effectiveness of empagliflozin added on to standard care (consisting of background antidiabetes medications and treatment of CV risk factors) versus standard care alone in T2DM patients with established CV disease, based on the trial population and results of the EMPA-REG OUTCOME study. The analysis was a patient-level simulation performed over a lifetime time horizon (40 years), and the perspective was that of a Canadian public payer.

The manufacturer's base-case analysis predicted that treatment with empagliflozin plus standard care was associated with 0.74 incremental quality-adjusted life-years (QALYs) at an incremental cost of \$4,447 compared with standard care alone, resulting in an incremental cost-utility ratio (ICUR) of \$5,977 per QALY. The probability that empagliflozin was cost-effective at a willingness-to-pay threshold of \$50,000 per QALY was more than 90%.

CDR identified the following key limitations with the manufacturer's economic submission:

- The CDR clinical review identified a number of methodological limitations related to the EMPA-REG OUTCOME trial, such as the rigour of outcome ascertainment, lack of control of type 1 error, and potential confounding after randomization. The limitations of the clinical data underlying the economic analysis cast uncertainty on the validity of the cost-effectiveness results.

- The choice of statistical distributions to extrapolate long-term event rates for outcomes modelled in the economic analysis was based on somewhat subjective considerations, such as clinical plausibility. However, CDR considered that these projections were relatively conservative with respect to the estimated cost-effectiveness of empagliflozin.
- The EMPA-REG OUTCOME trial data reflect the time to first event for each of the studied outcomes; therefore, the risks for subsequent events in the model were independent of prior events. However, a scenario analysis found that empagliflozin was likely to be cost-effective even under the conservative assumption that the drug had no benefit compared with standard care for subsequent events, although the ICUR was higher (approximately \$24,000 per QALY) than in the base-case analysis.
- The submitted analysis did not include mark-up and dispensing fees as part of total drug costs. Also, costs of blood glucose testing strips were not included. Inclusion of these omitted costs was expected to slightly increase the ICUR for empagliflozin compared with standard care.

Apart from the methodological limitations of the EMPA-REG OUTCOME trial and the associated uncertainty regarding the validity of the observed benefits of empagliflozin, CDR considered that the identified limitations of the submitted economic analysis were unlikely to have a significant impact on its conclusions. Therefore, CDR accepted the manufacturer's base-case results and concluded that empagliflozin was likely to be cost-effective for the reviewed indication.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeyesundera.

September 21, 2016 Meeting

Regrets:

Four CDEC members did not attend.

Conflicts of Interest:

None

About this Document:

CDEC provides formulary reimbursement recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

Common Drug Review

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