

# Drug Coverage Decision for B.C. PharmaCare

## About PharmaCare

B.C. PharmaCare is a government-funded drug plan. It helps British Columbians with the cost of eligible prescription drugs and specific medical supplies.

## Details of Drug Reviewed

<b>Drug</b>	<b>Empagliflozin; Empagliflozin-metformin</b>
Brand Name	Jardiance™; Synjardy®
Dosage Form(s)	10 mg, 25 mg tablets; 5 mg / 500 mg, 5 mg / 850 mg, 5 mg / 1000 mg, 12.5 mg / 500 mg, 12.5 mg / 850 mg, 12.5 mg / 1000 mg tablets
Manufacturer	Boehringer Ingelheim (Canada) Ltd.
<b>Submission Type</b>	<b>New Submission</b>
Use Reviewed	Treatment of type 2 diabetes mellitus (T2DM)
Common Drug Review (CDR)	Yes, CDR recommended: <b>to Reimburse with clinical criteria and/or conditions</b> . Visit the CDR website for more details: <a href="https://www.cadth.ca/about-cadth/what-we-do/products-services/cdr/reports">https://www.cadth.ca/about-cadth/what-we-do/products-services/cdr/reports</a>
Drug Benefit Council (DBC)	<p>DBC met on November 7, 2016 to review empagliflozin as an add-on therapy to standard diabetes care to reduce the incidence of cardiovascular (CV) death in patients with T2DM and established CV disease who have inadequate glycemic control.</p> <p>DBC considered various inputs including: the final reviews completed by the CDR on October 26, 2016, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC), CDR patient input, Clinical Practice Reviews from two specialists, and a Budget Impact Assessment. The DBC did not receive any Patient Input Questionnaire responses from patients, caregivers, or Patient Groups.</p> <p>DBC now screens drug submissions under review by the CDR to determine whether or not a full DBC review is necessary, based on past DBC reviews, recommendations, and existing PharmaCare coverage. If a full DBC review is determined to not be required, the Ministry's drug coverage decision will be based on the CDEC recommendation and an internal review only. The DBC screened empagliflozin and empagliflozin-metformin for third-line coverage and advised that because these drugs are similar to some of the other drugs used for the treatment of type 2 diabetes the Ministry may accept the CDEC's recommendations.</p>
<b>Drug Coverage Decision</b>	<b>Limited Coverage Benefit for empagliflozin. Access the empagliflozin criteria from <a href="http://www.gov.bc.ca/pharmacarespecialauthority">www.gov.bc.ca/pharmacarespecialauthority</a></b> <b>Non-Benefit for empagliflozin-metformin</b>
Date	May 27, 2019
Reason(s)	<ul style="list-style-type: none"> <li>Based on the evidence reviewed by the CDR empagliflozin demonstrated that it is superior to placebo for improving glycemic control, reducing body weight, and lowering systolic blood pressure (SBP) when used in combination with metformin and a sulfonylurea,</li> <li>CDR and the DBC reviewed evidence from 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</li> </ul>

	<p>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.</p> <ul style="list-style-type: none"> <li>• The DBC recommended not to fund empagliflozin for patients with established CV disease due to methodologic limitations as well as significant budget implications.</li> <li>• BC participated in the pan-Canadian Pharmaceutical Alliance negotiations with the manufacturers which were able to address some of the financial considerations.</li> </ul>
Other Information	None

### The Drug Review Process in B.C.

A manufacturer submits a request to the Ministry of Health (Ministry).

An independent group called the [Drug Benefit Council \(DBC\)](#) gives advice to the Ministry. The DBC looks at:

- whether the drug is safe and effective
- advice from a national group called the [Common Drug Review \(CDR\)](#)
- what the drug costs and whether it is a good value for the people of B.C.
- ethical considerations involved with covering or not covering the drug
- input from physicians, patients, caregivers, patient groups and drug submission sponsors

The Ministry makes PharmaCare coverage decisions by taking into account:

- the existing PharmaCare policies, programs and resources
- the evidence-informed advice of the DBC
- the drugs already covered by PharmaCare that are used to treat similar medical conditions
- the overall cost of covering the drug

Visit the [The Drug Review Process in B.C. - Overview](#) and [Ministry of Health - PharmaCare](#) for more information.

**This document is intended for information only.**

It does not take the place of advice from a physician or other qualified health care provider.

## Drug Benefit Council (DBC) Recommendation and Reasons for Recommendation

### FINAL

#### Empagliflozin (Jardiance™)

Boehringer Ingelheim (Canada) Ltd.

#### Description:

Drug review of **empagliflozin (Jardiance™)** for the following Health Canada approved indications:

As an add-on therapy to standard diabetes care to reduce the incidence of cardiovascular (CV) death in patients with type 2 diabetes mellitus (T2DM) and established CV disease who have inadequate glycemic control.

In their review, the DBC considered the following: the final reviews completed by the Common Drug Review (CDR) on October 26, 2016, which included clinical and pharmacoeconomic evidence review material and the recommendations from the Canadian Drug Expert Committee (CDEC). The DBC did not receive any Patient Input Questionnaire responses from patients, caregivers, or Patient Groups. The DBC also considered CDR patient input, Clinical Practice Reviews from two specialists, and a Budget Impact Assessment.

#### Dosage Forms:

Jardiance™ is available as empagliflozin 10 mg and 25 mg oral tablets.

#### Recommendations:

1. The Drug Benefit Council (DBC) recommends that empagliflozin not be listed.

#### Reasons for the Recommendation:

##### 1. Summary

- In one randomized, double-blind, noninferiority trial, add-on therapy with empagliflozin did not appear to increase the risk of major CV adverse events compared to standard care in patients with inadequate glycemic control of longstanding type 2 diabetes, and CV disease.
- The trial had significant methodological limitations that call into question the validity of the reported benefits of empagliflozin on the primary outcome. Due to the methodological limitations of the trial, the impact of empagliflozin on the primary outcome of major CV events is unclear.
- In absence of a superiority benefit, from a safety perspective the drug becomes noninferior to placebo.
- At the manufacturer submitted price, listing empagliflozin as a benefit would be a significant budget impact.

##### 2. Clinical Efficacy

- The DBC considered the CDR systematic review, which included one randomized, double-blind, noninferiority trial (EMPA-REG OUTCOME) designed to assess the CV safety of empagliflozin 10 mg and 25 mg daily versus placebo (as add on therapy to standard care), in patients with type 2 diabetes and high CV risk. EMPA-REG OUTCOME was designed predominately as a safety trial, not as an efficacy trial.
- The primary outcome was time to first occurrence of a major adverse cardiovascular event (MACE), including CV death, nonfatal myocardial infarction (MI) (excluding silent MI), or nonfatal stroke, and with a noninferiority margin of 1.3 for the hazard ratio (HR).
- Empagliflozin was non-inferior to placebo based on time to first occurrence of CV death, nonfatal myocardial infarction (MI) (excluding silent MI), nonfatal stroke and for the key secondary outcome, hospitalization for unstable angina. Superiority was achieved for the primary outcome but not achieved for the key secondary outcomes.
- Empagliflozin was non-inferior and superior to placebo for the three-point MACE outcome but not superior to placebo for the four-point MACE outcome.
- The EMPA-REG OUTCOME trial had significant methodological limitations:
  - The trial was designed to test the safety of empagliflozin, not to establish benefit on a specific outcome.
  - There was no adjudication of silent MI, microvascular or renal events. Results may be subject to bias due to the substantial proportion of patients who were excluded or missing from these outcomes.
  - Because there was no control for type I error across the numerous exploratory outcomes analyzed, including the individual components of the MACE primary outcome, some of the statistically significant differences may be the result of chance due to the high probability of type I errors.
  - Of the CV-related deaths, 40% were presumed CV death, as the events were unassessable. In sensitivity analyses excluding the unassessable deaths from the primary outcome, empagliflozin was noninferior to placebo, but was no longer superior.
- For detailed information on the systematic review of empagliflozin please see the CDEC Final Recommendation at: <https://www.cadth.ca/empagliflozin-0>.

### **3. Safety**

- Genital infections were reported more frequently in the empagliflozin groups compared to placebo, and were more common in women than men.
- The study was not designed to detect rare adverse events, such as diabetic ketoacidosis or lower limb amputation, which have been linked to sodium glucose transport protein (SLGT 2) inhibitors. The safety and efficacy of empagliflozin beyond 2.6 years of therapy is unknown.
- For detailed information on the safety and tolerability of empagliflozin, please see the CDEC Final Recommendations at the links above.

### **4. Economic Considerations**

- The CDR clinical review identified significant limitations related to the EMPA-REG OUTCOME trial, which are an important source of uncertainty regarding the cost-effectiveness of empagliflozin for the reviewed indication.
- At the manufacturer listed price, the cost of empagliflozin is similar to other SLGT-2 inhibitors and combination products; similar or more expensive than the various dipeptidyl peptidase-4 (DPP-4) inhibitors and DPP-4 plus metformin combination products; less expensive than the glucagon-like peptide-1 (GLP-1) receptor agonists; and significantly more expensive than the insulin secretagogues, sulfonylureas, thiazolidinediones (TZDs), and alpha-glucosidase inhibitors.
- PharmaCare's Budget Impact Analysis estimated that the three-year cost impact of listing empagliflozin is significant.

### **5. Of Note**

- The DBC did not receive any Patient Input Questionnaire responses from patients, caregivers, or Patient Groups. The CDR Patient Group submission indicated the majority of patients were concerned that daily fluctuations in blood sugar and weight gain were the most important aspects of diabetes to control.
- Fourteen of the patients reported having taken empagliflozin as part of a clinical trial. Patients who had taken empagliflozin reported it was effective in keeping blood sugar levels at target and decreasing side effects (including diarrhea, stomach ache, losing weight), while providing better quality of life.