Common Drug Review
Pharmacoeconomic Review Report

October 2016

Drug	Empagliflozin (Jardiance)
Indication	As an adjunct to diet, exercise and standard care therapy to reduce the incidence of cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease who have inadequate glycemic control
Listing request	As per indication
Dosage form (s)	10 mg and 25 mg tablets
NOC date	July 27, 2016.
Manufacturer	Boehringer Ingelheim (Canada) Ltd.

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

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ABBREVIATIONS

CDR	CADTH Common Drug Review
CV	cardiovascular
ICUR	incremental cost-utility ratio
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
UA	unstable angina

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	**Empagliflozin (Jardiance) 10 mg and 25 mg**
Study Question	The objective is to quantify the clinical and economic outcomes of empagliflozin for treatment of patients with T2DM at increased CV risk based on the EMPA-REG OUTCOME study.
Type of Economic Evaluation	CUA
Target Population	T2DM patients at high risk for CV events
Treatment	Starting dose of empagliflozin 10 mg oral tablet once daily that could be increased to 25 mg once daily.
Outcome	QALYs
Comparator	Standard care
Perspective	Canadian health care system
Time Horizon	Lifetime (40 years)
Results for Base Case	Compared to standard care: ICUR: $5,977 per QALY gained
Key Limitations	CDR identified the following limitations with the submitted analysis: • The CDR clinical review identified a number of limitations related to the EMPA-REG OUTCOME trial that call into question the validity of the reported benefits of empagliflozin. This represents an important source of uncertainty regarding the cost-effectiveness of empagliflozin for the reviewed indication. • The manufacturer fitted parametric distributions to the EMPA-REG OUTCOME trial data to extrapolate long-term event rates for each modelled outcome. The choice of distributions was somewhat subjective since a number of alternative distributions provided adequate statistical fit to the data. The submitted model did not permit selection of alternate distributions. • Blindness and amputation were not included in the model, even though these were specified end points in the EMPA-REG OUTCOME trial. • The risk of subsequent events in the model was assumed to be independent of prior events, which is unlikely in real-world practice. • The submitted economic model compared empagliflozin to standard care (i.e., placebo from trial) but did not include the costs and disutilities associated with hypoglycemia associated with empagliflozin. • Mark-up and dispensing fees were not included as part of the total drug costs in the model. Also, the costs of blood glucose testing strips were not included.
CDR Estimate(s)	The limitations identified by CDR did not substantially impact the estimated ICUR; therefore, CDR accepted the manufacturer's base-case results and did not perform an alternative base-case reanalysis.

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; CV = cardiovascular; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; T2DM = type 2 diabetes mellitus.

EXECUTIVE SUMMARY

Background

Empagliflozin (Jardiance) is a once daily, oral antidiabetic drug belonging to the sodium-glucose cotransporter-2 (SGLT-2) inhibitor class. It exerts its effect by promoting urinary glucose excretion. Empagliflozin is currently indicated for the treatment of type 2 diabetes mellitus (type 2 diabetes) in conjunction with diet and exercise, as monotherapy, or as add-on therapy to other oral antidiabetic treatments or insulin.[1]

This report will review empagliflozin when indicated 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 and established CV disease who have inadequate glycemic control.[2]

The recommended dose of empagliflozin is 10 mg once daily. The dose can be increased to 25 mg once daily in patients who tolerate empagliflozin but who need additional glycemic control.[2] The manufacturer submitted a price of $2.6177 per 10 mg or per 25 mg tablet ($2.62 daily).[1]

Empagliflozin was previously reviewed by the Common Drug Review (CDR) and received a positive listing recommendation by the Canadian Drug Expert Committee (CDEC) in October 2015 as treatment for adults with type 2 diabetes to improve glycemic control in combination with metformin and a sulfonylurea when diet, exercise, and dual therapy (with metformin plus a sulfonylurea) do not provide adequate glycemic control, under the condition that the drug plan cost for empagliflozin not exceed the cost of the least expensive option among SGLT-2 and DPP-4 inhibitors.[3]

The manufacturer submitted an economic evaluation based on the results of the EMPA-REG OUTCOME trial to determine the cost-effectiveness of empagliflozin added on to standard care (consisting of background antidiabetes medications and treatment of CV risk factors, as per the EMPA-REG OUTCOME trial) versus standard care alone in type 2 diabetes patients at high CV risk. The analysis was performed over a lifetime time horizon (40 years), and the perspective was that of a Canadian public payer. Clinical events captured in the model were based on end points specified in the EMPA-REG OUTCOME protocol[4] and included non-fatal myocardial infarction (MI); non-fatal stroke; unstable angina (UA); hospitalization for heart failure (HF), transient ischemic attack (TIA), revascularization, CV death, development of macroalbuminuria, renal injury, and renal failure. Utilities and Canadian costs for managing complications were obtained from published sources.

Summary of Identified Limitations and Key Results

In the base case, the manufacturer predicted 0.74 incremental quality-adjusted life-years (QALYs) at an incremental cost of $4,447 for empagliflozin plus standard care, resulting in an incremental cost-utility ratio (ICUR) of $5,977 per QALY versus standard care .[1] The results of the manufacturer's sensitivity analyses indicated that the cost-effectiveness of empagliflozin was most affected when empagliflozin had no benefit on the risk of modelled CV events after the first event; the ICUR increased to $24,201 per QALY in this scenario.

CADTH Common Drug Review (CDR) identified several limitations with the submitted economic analysis. The CDR clinical review identified a number of limitations related to the EMPA-REG OUTCOME trial that call into question the validity of the reported benefits of empagliflozin. This represents an important source of uncertainty regarding the cost-effectiveness of empagliflozin for the reviewed indication.

Another limitation was related to the selection of survival curves to extrapolate event rates from the EMPA-REG OUTCOME trial over a lifetime time horizon, particularly the inability to select alternative curves to test the robustness of the base-case results. Another shortcoming was that the model does not allow the user to specify a population at lower CV risk than was included in the EMPA-REG OUTCOME trial. This is an important limitation in the event that empagliflozin is used off-label in patients at CV risk but without established CV disease; treatment of such patients is likely to be less cost-effective, as there would be smaller absolute benefits of empagliflozin in terms of events avoided. None of the other limitations identified by CDR were expected to have a substantial impact on the estimated ICUR.

Conclusions

Model limitations identified by CDR did not have a substantial impact on the estimated ICUR; therefore, CDR accepted the manufacturer's base-case result and did not perform an alternative base-case analysis. The manufacturer reported a base-case ICUR of $5,977 per QALY for empagliflozin plus standard care compared with standard care in patients at high CV risk reflective of the EMPA-REG OUTCOME trial population. The probability that empagliflozin was cost-effective at a willingness-to-pay threshold of $50,000 per QALY was more than 90%. The CDR clinical review identified significant limitations related to the EMPA-REG OUTCOME trial; this represents an important source of uncertainty regarding the cost- effectiveness of empagliflozin for the reviewed indication.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PE SUBMISSION

The manufacturer submitted a cost-utility model of empagliflozin added on to standard care versus standard care alone in patients with type 2 diabetes at high cardiovascular (CV) risk. A patient-level simulation based on risk equations derived using patient-level data from the EMPA-REG OUTCOME trial was used to compare the long-term effects of empagliflozin added to standard care (consisting of background antidiabetes medications and treatment of CV risk factors, as per the EMPA-REG OUTCOME trial) with standard care alone in patients at high CV risk. The model simulated 5,000 patients over a lifetime horizon (40 years), with costs and quality-adjusted life-years (QALYs) discounted at 5%. The perspective of the analysis was that of a Canadian public payer.

The EMPA-REG OUTCOME study was a multi-centre, double-blind (DB), placebo-controlled, randomized controlled trial (RCT) that examined the effects of empagliflozin added to standard care compared to standard care alone on CV morbidity and mortality in a population with type 2 diabetes at high risk for CV events. Patients had been previously treated with standard care for type 2 diabetes. The primary outcome of the EMPA-REG OUTCOME trial was a composite of death from CV causes, non-fatal myocardial infarction (MI), and non-fatal stroke. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina (UA). Clinical events captured in the model were based on end points specified in the EMPA-REG OUTCOME protocol[4] and included non-fatal MI, non-fatal stroke, unstable angina (UA), hospitalization for heart failure (HF), transient ischemic attack (TIA), revascularization, CV death, development of macroalbuminuria, renal injury (defined as a doubling of serum creatinine, with eGFR < 45 mL/min), and renal failure (defined as need for renal replacement therapy). Time-dependent parametric survival analyses of the EMPA-REG OUTCOME trial data were conducted to characterize clinical event rates over time with and without empagliflozin. The manufacturer fitted a parametric distribution to the EMPA-REG OUTCOME trial data for each modelled outcome by testing various statistical distributions (i.e., exponential, Weibull, log-normal, log-logistic, and Gompertz) and assessing fit over the observed data period and beyond. The Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were compared to determine best fit (with lower values indicating better fit), and plots of observed versus predicted outcome distributions were produced to assess goodness-of-fit. Selection of an optimal distribution for each outcome involved both statistical (e.g., goodness-of-fit, avoidance of over-fitting) and clinical (e.g., plausibility of projected event rates) considerations.

The model begins with the creation of simulated patient profiles. Each profile is cloned and one clone is assigned to each comparator (empagliflozin and standard care). Next, predicted time to event is assigned for each of 10 possible events based on statistical extrapolations of event rates from EMPA-REG OUTCOME. Each simulated patient experiences the earliest of these events, and the model steps forward in time to that event. If that event is terminal (death or end of the model time horizon), the event, cost, and QALY results for the patient are stored and the model moves to the next patient. If the event is non-fatal, the risk of future events and the predicted times to events are updated. The earliest event is again selected and the process repeats until a fatal event is experienced. Once all patients have been simulated on both treatments, the results are summed to compute the overall cost-effectiveness of empagliflozin versus standard care. Patients who do not die of CV causes have their survival predicted by Canadian life tables.[1]

The costs of managing clinical events were based on published literature,[5,6] and are inflated to February 2016 Canadian dollars. Long-term costs associated with modelled events were excluded in the model to avoid double-counting future event costs. Patients' quality of life at baseline and utility decrements associated with each event are based on a study by Sullivan et al. (2015) that provided a fixed decrement in utility for each event type along with a rule for combining decrements as patients accumulate multiple diabetes-related complications.[7] The utility decrements for a urinary tract infections (UTIs) and genital infections were sourced from published literature.[8]

2. MANUFACTURER'S BASE CASE

The manufacturer's base-case results are summarized in Table 2.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	EMPAGLIFLOZIN	STANDARD CARE	INCREMENTAL
Life-years (undiscounted)[a]	14.5	12.3	2.18
QALYs	7.19	6.44	0.74
Total costs ($)	43,662	39,214	4,447
Drug costs ($)	8,978	0	8,978
Event costs ($)	34,683	39,214	–4,532
ICUR ($)	5,977/QALY		
NMB at WTP of $50,000 per QALY ($)	32,753 per patient		

ICUR = incremental cost-utility ratio; NMB = net monetary benefit; QALY = quality-adjusted life-year; WTP = willingness-to-pay.
[a] Costs, QALYs, and NMB are discounted at an annual rate of 5%, but life-years are not.
Source: Manufacturer's pharmacoeconomic report, table 9, page 11.[1]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The results of the manufacturer's sensitivity analyses indicated that the cost-effectiveness of empagliflozin was most affected when it was assumed that empagliflozin had no benefit on the risk of modelled events after the first event; the ICUR increased to $24,201 per QALY in this scenario. In all other one-way sensitivity analyses that varied the model parameters (time horizon, population, clinical, cost, and utility inputs) the results were generally robust, with the ICUR ranging from $2,694 to $13,808 per QALY.

The manufacturer conducted a probabilistic sensitivity analysis (PSA) using 500 replications of 1,000 patients each. The results of the PSA indicated broad 95% confidence intervals around the event rates for both the empagliflozin and standard care groups, resulting in an ICUR ranging from $2,668 to $11,372 per QALY. The manufacturer's explanation for the relatively broad range of ICURs in the PSA was the lower number of patients simulated in the PSA compared with the base-case analysis (i.e., 1,000 versus 5,000), which resulted in greater variability in the predicted event rates. The cost-effectiveness acceptability curve (CEAC) showed that at a willingness-to-pay threshold of $50,000 per QALY, empagliflozin had a 99.6% probability of being cost-effective compared with standard of care.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Validity of clinical data:** The CADTH Common Drug Review (CDR) clinical review identified a number of 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 conclusion of the review was that empagliflozin may reduce CV mortality based on the results of an exploratory (rather than a primary or secondary) analysis, but that the impact of empagliflozin on MI, stroke, hospitalization for HF, renal, or other microvascular outcomes was unclear. The limitations of the available clinical data cast uncertainty on the validity of the cost-effectiveness results.
- **Long-term extrapolation of clinical outcomes:** The manufacturer fitted a parametric distribution to the EMPA-REG OUTCOME trial data to extrapolate long-term event rates for each outcome; distributions were selected based on both statistical and clinical considerations, as well as on goodness-of-fit in relation to the observed data and the plausibility of results. Diagnostic plots associated with the various distributions fitted to the outcomes of interest showed that multiple distributions provided good fit, with relatively little distinction between the AIC and BIC values for different distributions. However, in many cases, there were marked differences between alternative distributions in predicted event rates for several outcomes, especially at distant time points. Due to the lack of statistical differentiation between various distributions, the choice of distribution was ultimately based on relatively subjective considerations such as the clinical plausibility of long-term projections and the simplicity of the fitted form. The submitted economic model incorporated only the selected distribution for the outcome of interest, and did not permit the user to test the impact of using alternative distributions. However, the manufacturer's selected distributions were generally intermediate with respect to the predicted long-term event rates for most outcomes, and therefore somewhat conservative in terms of the estimated cost-effectiveness of empagliflozin. Furthermore, the ICUR for empagliflozin was similar to the base-case result even under the most conservative time horizon scenario of three years (which reflects actual EMPA-REG OUTCOME data and avoids the need for extrapolation), which somewhat mitigates the concerns regarding selection of distributions. Nevertheless, the opportunity to examine the impact of distribution choice would have been desirable to confirm the robustness of the manufacturer's base-case result.
- **Blindness and amputation not included as events:** The manufacturer indicated that the included clinical events in the model were based on end points specified in the EMPA-REG OUTCOME study; blindness and amputation were end points in the trial, but were not included in the model even though information on the prevalence, costs, and disutilities associated with blindness and amputation in patients with type 2 diabetes is available in the published literature.[9] However, the impact of omitting these outcomes on the estimated ICUR is expected to be minimal.
- **Hypoglycemia events associated with treatment use not included:** The submitted economic model did not include the costs and disutilities associated with empagliflozin-related hypoglycemia (severe and non-severe). However, the impact of this factor on the ICUR is likely negligible due to the similar rates of confirmed hypoglycemia observed in the standard care and empagliflozin groups in the EMPA-REG OUTCOME study (28% in both groups).[4]
- **Mark-up, dispensing fees, and test strip costs not included:** 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 is expected to slightly increase the ICUR for empagliflozin compared with standard care due to an increase in incremental costs.
- **Subsequent events:** As the EMPA-REG OUTCOME trial data reflects the time to first event for each of the studied outcomes, the risks for subsequent events in the model are independent of prior events. For example, the occurrence of stroke as the first event does not increase the risk of a subsequent

stroke in the model. This may not reflect real-world practice, as the risk of subsequent events may be higher. However, this concern is mitigated somewhat by the fact that all patients in the EMPA-REG OUTCOME trial had established CV disease (76% had coronary artery disease, 47% had a prior MI, and 23% had a prior stroke); thus, the data from the trial at least partially reflects a secondary prevention population. As well, the manufacturer's scenario analysis found that empagliflozin was likely to be cost-effective even under the conservative assumption that the drug had no benefit over standard care for subsequent events, although the ICUR was considerably higher in this scenario (~$24,000/QALY) than in the base-case analysis.

- **Empagliflozin for patients with type 2 diabetes at lower CV risk:** An analysis assessing the cost-effectiveness of empagliflozin in type 2 diabetes patients at lower CV risk compared with the type 2 diabetes patients at higher CV risk who were studied in the EMPA-REG OUTCOME trial would have been desirable, as there is the potential for off-label use of empagliflozin in a broader population of patients than those included in the trial. However, due to data and technical limitations, the submitted model does not permit the user to perform such an analysis. Empagliflozin is expected to be less cost-effective in lower-risk patients due to the smaller absolute number of CV events likely to be experienced by such patients.

5. CADTH COMMON DRUG REVIEW REANALYSES

Due to limitations with the submitted economic model, CDR was not able to conduct a reanalysis using alternative parametric distributions to fit the trial data for each clinical outcome. The remaining limitations identified by CDR were deemed to have had minimal impact on the manufacturer's base-case ICUR result; therefore, CDR accepted the manufacturer's base-case results.

6. ISSUES FOR CONSIDERATION

The approved indication for empagliflozin requires that patients have established CV disease. According to the clinical expert consulted by CDR for this review, however, there may be variability in clinical practice in how patients with type 2 diabetes are classified as being at high CV risk for the purpose of determining the appropriateness of empagliflozin therapy. Therefore, the potential exists for the use of empagliflozin in patients with diabetes and CV risk factors who do not have established CV disease. The cost-effectiveness of empagliflozin in lower-risk patients could not be determined from the model submitted by the manufacturer.

7. PATIENT INPUT

Input was received from the Canadian Diabetes Association (CDA), which solicited patient input through two previous surveys regarding experiences with current drug therapies. These surveys had been distributed through social media and email blasts for a previous CDR submission for empagliflozin. The first survey was conducted in August 2014 and included responses from 376 patients and their caregivers, while the second survey was conducted in April 2015 and gathered information from 424 individuals (349 patients with diabetes and 75 caregivers). Approximately 4% of patients (14 of 349 respondents) had taken empagliflozin. Patients who had taken empagliflozin noted its effectiveness in keeping blood sugar levels at target, its reduced side effects (diarrhea, stomach ache, weight loss), and its ability to provide a "better quality of life" from their perspective. The manufacturer's economic submission captured quality of life while on empagliflozin based on its impact on CV events, but did not

model all adverse events (AEs) associated with antidiabetic therapy (i.e., hypoglycemia). However, this omission was unlikely to have had a significant impact on ICUR results.

8. CONCLUSIONS

Model limitations identified by CDR did not have a substantial impact on the estimated ICUR; therefore, CDR accepted the manufacturer's base-case result and did not perform an alternative base-case analysis. The manufacturer reported a base-case ICUR of $5,977 per QALY for empagliflozin plus standard care compared with standard care in patients at high CV risk reflective of the EMPA-REG OUTCOME trial population. The probability that empagliflozin was cost-effective at a willingness-to-pay threshold of $50,000 per QALY was more than 90%. The CDR clinical review identified significant limitations related to the EMPA-REG OUTCOME trial; this represents an important source of uncertainty regarding the cost-effectiveness of empagliflozin for the reviewed indication.

APPENDIX 1: COST COMPARISON

The comparators presented in the tables below have been deemed to be appropriate by the clinical expert consulted by the Common Drug Review (CDR). Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the tables, and as such may not represent the actual costs to public drug plans.

TABLE 3: COST COMPARISON TABLE OF ANTIDIABETIC TREATMENTS INDICATED FOR CV RISK REDUCTION IN PATIENTS WITH TYPE 2 DIABETES

DRUG/ COMPARATOR	STRENGTH	DOSAGE FORM	PRICE ($)	RECOMMENDED DOSE	AVERAGE DAILY DRUG COST ($)	AVERAGE ANNUAL DRUG COST ($)
SGLT-2 inhibitors						
Empagliflozin (Jardiance)	10 mg 25 mg	tab	2.6177[a]	10 mg or 25 mg daily	2.62	956

SGLT-2 = sodium-glucose cotransporter-2.
[a] Manufacturer's submission price.[1]

TABLE 4: COST COMPARISON TABLE FOR NON-INSULIN ANTIDIABETIC AGENTS

DRUG/ COMPARATOR	STRENGTH	DOSAGE FORM	PRICE ($)	RECOMMENDED DOSE	AVERAGE DAILY DRUG COST ($)	AVERAGE ANNUAL DRUG COST ($)
SGLT-2 inhibitors						
Canagliflozin (Invokana)	100 mg 300 mg	tab	2.6960	100 mg or 300 mg daily	2.70	986
Dapagliflozin (Forxiga)	5 mg 10 mg	tab	2.4500[a]	5 mg or 10 mg daily	2.45	894
SGLT-2 inhibitors/Metformin combination products						
Dapagliflozin/ Metformin (XigDuo)	5 mg/850 mg 5 mg/1,000 mg	tab tab	1.2250[c,d] 1.2250[c,d]	BID BID	2.4500 2.4500	894
Biguanides						
Metformin	500 mg 850 mg	tab	0.0444 0.0610[b]	500 mg, three to four times daily	0.18 to 0.23	49 to 65
DPP-4 inhibitors						
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	tab	2.1000[a]	25 mg daily	2.10	767
Linagliptin (Trajenta)	5 mg	tab	2.5500	5 mg daily	2.55	931
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	tab	2.3997 2.8753	5 mg daily	2.88	1,049

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Sitagliptin (Januvia)	25 mg 50 mg 100 mg	tab	2.9790	100 mg daily	2.98	1,087
DPP-4 inhibitor plus metformin fixed-dose combinations						
Alogliptin/ metformin (Kazano)	12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	tab	1.1450[a]	Two tablets daily	2.29	836
Linagliptin/ metformin (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	tab	1.3337	Two tablets daily	2.67	974
Saxagliptin/ metformin (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	tab	1.2700	Two tablets daily	2.54	927
Sitagliptin/ metformin (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	tab	1.6159	Two tablets daily	3.23	1,180
GLP-1 receptor analogue						
Dulaglutide (Trulicity)	0.75 mg/0.5 mL 1.5 mg/0.5 mL	4 × 0.5 mL pre-filled pen	191.8000[c]	0.75 mg to 1.5 mg once weekly	6.85	2,493
Exenatide (Bydureon)	2 mg	2 mg pre-filled pen	47.9400[c]	2 mg once weekly	6.85	2,493
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/ mL)	119.7250[c]	5 mcg to 10 mcg twice daily	3.99	1,457
Liraglutide (Victoza)	2 × 3 mL 3 × 3 mL	Pre-filled pen (6 mg/mL)	136.98[a] 205.47[a]	1.2 mg to 1.8 mg daily	4.57 to 6.85	1,667 to 2,500
Sulfonylureas						
Gliclazide (generics)	80 mg	tab	0.0931	80 mg to 320 mg daily (in divided doses of > 160 mg daily)	0.09 to 0.37	34 to 136
Gliclazide long-acting (Diamicron MR)	30 mg 60 mg	ER tab	0.0931 0.2150	30 mg to 120 mg daily	0.09 to 0.43	34 to 157
Glimepiride (generics)	1 mg 2 mg 4 mg	tab	0.3857[a]	1 mg to 4 mg daily	0.39	142

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Glyburide (generics)	2.5 mg 5.0 mg	tab	0.0321 0.0574	2.5 mg to 20 mg daily (in divided doses of > 10 mg daily)	0.03 to 0.23	12 to 84
TZDs						
Pioglitazone (generics)	15 mg 30 mg 45 mg	tab	0.3800[e] 0.5360[e] 0.8075[e]	15 mg to 45 mg daily	0.38 to 0.81	139 to 295
Rosiglitazone (Avandia)	2 mg 4 mg 8 mg	tab	1.3755[e] 2.1584[e] 3.0865[e]	4 mg to 8 mg daily	2.16 to 3.09	788 to 1,126
Rosiglitazone / metformin (Avandamet)	2/500 mg 4/500 mg 2/1,000 mg 4/1,000 mg	tab	1.1959[e] 1.6424[e] 1.3062[e] 1.7857[e]	4/1,000 mg to 8/2,000 mg daily in divided doses	2.39 to 3.57	873 to 1,304

DPP-4 = Dipeptidyl peptidase-4; ER = extended release; GLP-1 = glucagon-like peptide-1; tab = tablet; SGLT-2 = sodium-glucose cotransporter-2; TZDs = thiazolidinediones.
[a] Régie de l'assurance maladie du Québec (RAMQ), May 2016.[10]
[b] Alberta Drug Formulary (June 2016).[11]
[c] DeltaPA, manufacturer's list price, accessed June 2016.[12]
[d] Price shown is for Quebec. Listed unit price is $1.31 in most other provinces.[12]
[e] Saskatchewan Drug Formulary (June 2016).[13]
Source: Ontario Drug Benefit (May 2016) prices unless otherwise indicated.[14]

Table 5: Cost Comparison of Insulin Agents

Drug/Comparator	Strength	Dosage Form	Price ($)	Cost per mL ($)
Short-acting insulins				
Insulin aspart (NovoRapid)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	58.81 61.21 29.00	3.92 4.08 2.90
Insulin glulisine (Apidra)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	51.10 51.70 25.68	3.41 3.45 2.57
Insulin lispro (Humalog)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	56.38 55.27 28.02	3.76 3.68 2.80
Regular human insulin (Humulin R)	100 U/mL	5 × 3 mL cartridge 10 mL vial	45.12 22.99	3.01 2.30
Regular human insulin (Novolin ge Toronto)	100 U/mL	5 × 3 mL cartridge 10 mL vial	44.38 22.61	2.96 2.26
Insulin NPH				
Humulin N	100 U/mL	5 × 3 mL cartridge 10 mL vial	45.12 22.99	3.01 2.30
Novolin ge NPH	100 U/mL	5 × 3 mL cartridge 10 mL vial	45.44 23.12	3.03 2.31

DRUG/COMPARATOR	STRENGTH	DOSAGE FORM	PRICE ($)	COST PER ML ($)
Long-acting insulin analogues				
Insulin glargine (Lantus)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	92.85 92.85 61.69	6.19 6.19 6.17
Insulin glargine (Basaglar)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL pre-filled pen	78.92[a] 78.92[a]	5.26 5.26
Insulin detemir (Levemir)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	107.82 107.82	7.19 7.19
Pre-mixed insulins				
Biphasic insulin aspart 30/70 (NovoMix 30)	100 U/mL	5 × 3 mL cartridge	55.37	3.69
Lispro/lispro protamine 25/75 (Humalog Mix 25)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	56.65 55.92	3.78 3.73
Lispro/lispro protamine 50/50 (Humalog Mix 50)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	55.48 54.99	3.70 3.67
Humulin 30/70	100 U/mL	5 × 3 mL cartridge 10 mL vial	45.12 22.99	3.01 2.30
Novolin ge 30/70	100 U/mL	5 × 3 mL cartridge 10 mL vial	44.91 23.24	2.99 2.32
Novolin ge 40/60	100 U/mL	5 × 3 mL cartridge	45.24	3.02
Novolin ge 50/50	100 U/mL	5 × 3 mL cartridge	45.24	3.02

DeltaPA, manufacturer's list price, accessed June 2016[12]
Source: Ontario Drug Benefit (May 2016) prices.[14]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS EMPAGLIFLOZIN RELATIVE TO THE PLACEBO?

EMPAGLIFLOZIN VERSUS PLACEBO	ATTRACTIVE	SLIGHTLY ATTRACTIVE	EQUALLY ATTRACTIVE	SLIGHTLY UNATTRACTIVE	UNATTRACTIVE	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	$5,977 per QALY[a]					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
[a] Based on manufacturer's pharmacoeconomic analysis.[1]

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 7: SUBMISSION QUALITY

	YES/ GOOD	SOMEWHAT/ AVERAGE	NO/ POOR
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

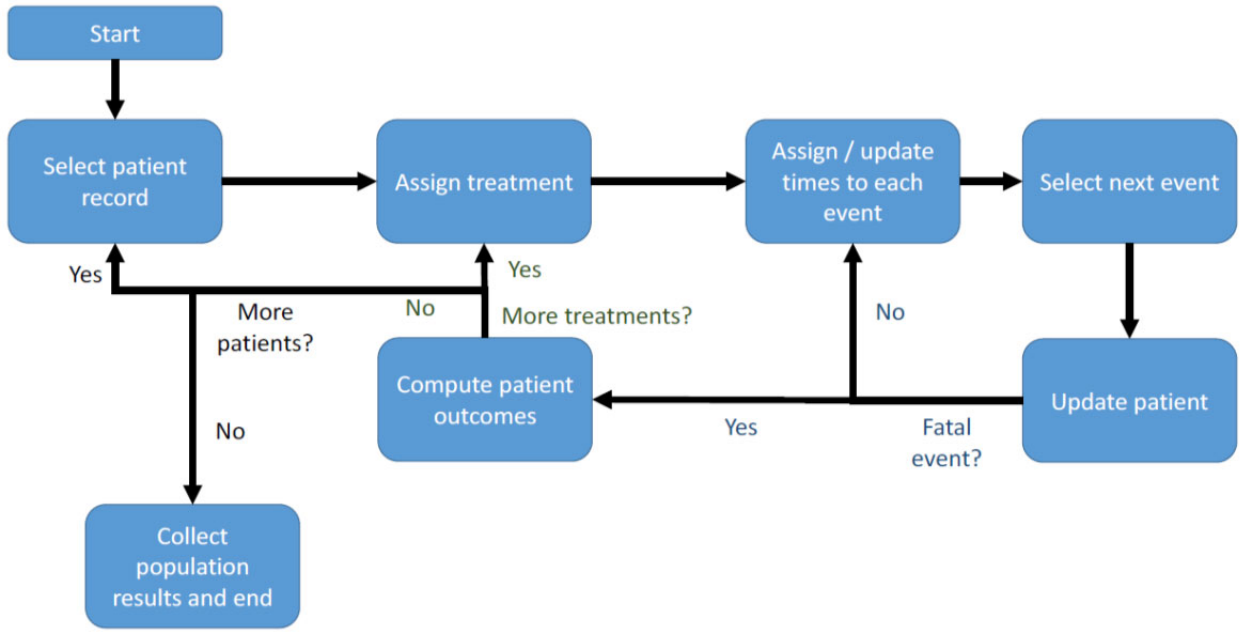
TABLE 8: AUTHORS' INFORMATION

AUTHORS OF THE PHARMACOECONOMIC EVALUATION SUBMITTED TO CDR			
☒ Adaptation of Global model/Canadian model done by the manufacturer ☐ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis		X	

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

FIGURE 1: MANUFACTURER'S MODEL DIAGRAM



Source: Manufacturer's pharmacoeconomic submission.[1]

TABLE 9: DATA SOURCES

DATA INPUT	DESCRIPTION OF DATA SOURCE	COMMENT
Clinical event rates	Time-dependent parametric survival analyses of the EMPA-REG OUTCOME trial data were conducted to characterize clinical event rates over time with empagliflozin plus standard of care.[4] Parametric distributions were fitted to the event data for each outcome to extrapolate event rates beyond the time horizon of the trial. The distributions were selected based on both statistical and clinical considerations, as well as goodness-of-fit in relation to the observed data and clinical plausibility of results.	When the diagnostic plots associated with the various distributions fitted to the outcomes of interest showed that multiple distributions provided good fit, the choice of distribution was ultimately based on relatively subjective considerations such as the clinical plausibility of long-term projections and the simplicity of the fitted form.
Patient population	Patient profiles were sourced from the EMPA-REG OUTCOMES trial and were simulated in the model.[4]	A trial patient can be sampled for the simulation multiple times. The model allows for additional and alternative patient records to be used.

Data Input	Description of Data Source	Comment
Utilities	• Baseline patient quality of life and utility decrements associated with each clinical event due to T2DM complications were primarily sourced from a study by Sullivan et al. (2015).[7] • Utility decrements for a UTI and GTI were sourced from Barry et al. (1997).[8] • Utility values from the CADTH Therapeutic Reviews of diabetes therapies were used in scenario analyses.[9]	According to the manufacturer, the Sullivan et al. study provided a fixed decrement in utility for each event type, along with a rule for combining decrements as patients accumulated multiple T2DM complications.
Mortality	Non-CV mortality was estimated using Canadian life tables.[1]	No additional information on the life tables or references was provided in the report.
Resource Use		
AEs (Indicate which specific AEs were considered in the model.)	Only UTIs and GTIs were included in the model as AEs.	Hypoglycemia (severe and non-severe) was not included in the model. As severe hypoglycemia is likely to be rare with empagliflozin, the impact on ICUR of omitting hypoglycemia is likely minimal.
Costs		
Drug	Provided by the manufacturer.[1]	
Event	Costs associated with each diabetes complication were taken from the publications by Goeree et al. (2009) and Smolderen et al. (2010) and expressed in 2015 Canadian dollars by inflating the costs using the Canadian Consumer Price Index.[5,6]	
AEs	Only the costs of UTI and GTI events were included in the model.	Costs associated with managing treatment-related hypoglycemia (severe and non-severe) were not included in this analysis. However, this is unlikely to have had a major impact on ICUR, due to the relative rarity of severe hypoglycemia with empagliflozin.

AE = adverse event; CV = cardiovascular; GTI = genital infection; ICUR = incremental cost-utility analysis; T2DM = type 2 diabetes mellitus; UTI = urinary tract infection;

TABLE 10: MANUFACTURER'S KEY ASSUMPTIONS

ASSUMPTION	COMMENT
The clinical event rates observed in clinical practice will mirror those observed in EMPA-REG OUTCOME.	**Appropriate (for subgroup of real-world patients at similarly high CV risk as EMPA-REG OUTCOME cohort)**
The EMPA-REG OUTCOME trial data reflect the time to first event for each of the clinical outcomes. Therefore, the risks for subsequent events in the model are independent of prior events.	**Likely appropriate.** Although the real-world practice risk of subsequent events after a first event may be higher, all patients in the EMPA-REG OUTCOME trial had established CV disease (76% had coronary artery disease, 47% had a prior MI, and 23% had had a prior stroke); thus, the data from the trial at least partially reflects a secondary prevention population.
The effects of aging and unmodelled comorbidities are captured in the shapes of the statistical extrapolations.	**Appropriate**
The effects of rare diabetic complications, such as blindness and amputation, are small.	**Likely appropriate.** Data on the costs and disutilities associated with blindness and amputation are available in the published literature, and could have been included in the submitted model for completeness.
Clinical events result in one-time costs only.	**Likely appropriate.** Although the manufacturer avoided the risk of double- counting associated with considering long-term costs of events, it is expected that clinical events will require ongoing care in some cases, and thus will incur continuous costs. The manufacturer explored the costs of future long-term events in sensitivity analyses.
The treatment effect of empagliflozin on each event type is conserved across subpopulations.	**Appropriate**
Patients who do not die of CV causes have survival predicted by Canadian life tables.	**Appropriate**

CV = cardiovascular; ICUR = incremental cost-utility ratio; MI = myocardial infarction; T2DM = type 2 diabetes.

Validation

The manufacturer undertook a technical validation of the model by running the model for a three-year time horizon to match the time horizon of the EMPA-REG OUTCOME trial. This approach validated that the derived equations reproduced the observed event rates in the trial. Absolute events rates and hazard ratios generally agreed with the trial results. The largest discrepancies were in the rates of revascularization, non-fatal stroke, and death from all causes, which were associated with rate ratios from the model that were slightly less favourable to empagliflozin than suggested by the observed data.

Monte Carlo Error and Convergence

The manufacturer investigated the Monte Carlo error and the number of simulations required to achieve convergence by running the model on different numbers of patients, ranging from 5 to 16,000 for both lifetime and trial duration time frames. Findings indicated that with a lifetime horizon, the model converges at a relatively low number of patients, while with the trial duration there is considerably more Monte Carlo error, and a higher number of simulations is required to generate stable results (Figure 2).

FIGURE 2: MONTE CARLO ERROR WITH NUMBER OF PATIENTS SIMULATED OVER TWO TIME HORIZONS

Source: Manufacturer's pharmacoeconomic submission.[1]

Manufacturer's Results

Based on the Monte Carlo error and convergence analysis, the manufacturer simulated 5,000 patients over a lifetime horizon in the base case. Patients in the empagliflozin group survived a mean of 14.5 years compared with 12.3 years in the standard care group. Patients receiving empagliflozin experienced lower rates of all clinical events except non-fatal stroke, hospitalization for unstable angina (UA), and non-CV-related mortality (Table 11).

TABLE 11: CLINICAL EVENTS (PER 100 PATIENT-YEARS)

EVENT	EMPAGLIFLOZIN	STANDARD CARE
Non-fatal MI	1.93	2.25
Non-fatal stroke	1.31	1.02
UA	1.29	1.25
HF	1.87	2.83
TIA	0.25	0.29
Revascularization	2.56	2.78
CV death	3.59	5.23
Development of macroalbuminuria	5.22	6.29
Renal injury	1.03	1.58
Renal failure	0.31	0.53

CV = cardiovascular; HF = heart failure; MI = myocardial infarction; TIA = transient ischemic attack; UA = unstable angina.
Source: Manufacturer's pharmacoeconomic submission, table 8, page 11.[1]

The longer survival and reduced rate of clinical events translates to an incremental 0.74 QALYs (7.19 with empagliflozin versus 6.44 with standard of care). Clinical event costs were reduced by $4,532 per patient despite the longer survival, partially offsetting the cost of empagliflozin ($8,978 per patient) to yield a net incremental cost of $4,447 per patient. This yielded an incremental cost-effectiveness ratio (ICUR) of $5,977 per quality-adjusted life-year (QALY), with a net monetary benefit at a willingness-to-pay of $50K per QALY of $32,753 per patient.

Manufacturer's Scenario Analyses

The manufacturer conducted several scenario analyses, which are summarized in Table 12.

TABLE 12: SUMMARY RESULTS OF MANUFACTURER SCENARIO ANALYSES

SCENARIO		INCREMENTAL COST ($)	INCREMENTAL QALYS	ICUR ($)
Model Setup				
Time Horizon	10 years	3,553,497	1,122	3,166
Discount rate: cost	0.0%	51,325,724	3,717	13,808
	3.5%	28,199,864	3,722	7,577
Discount rate: health	0.0%	22,243,057	8,255	2,694
	3.5%	22,241,727	4,663	4,770
Discount rate: cost and health	0.0%	51,325,184	8,237	6,231
	3.5%	28,207,011	4,646	6,071
Population Inputs				
Patient population	BCV1 (history of stroke)	25,946,072	3,720	6,974
	BCV2 (history of MI)	19,915,093	4,165	4,781
	BCV6 (PAD)	16,747,025	3,853	4,346
Clinical Inputs				
Baseline adjustment/HR[a]	10% decrease	23,387,064	3,542	6,602
	10% increase	21,228,147	3,887	5,461
Cost Inputs				
Drug cost: Empagliflozin	20% decrease	13,288,093	3,724	3,568
	20% increase	31,262,695	3,723	8,396
Event cost	20% decrease	26,774,336	3,724	7,189
	20% increase	17,706,300	3,725	4,753
Utility Inputs				
Utility, no event history[b]	20% decrease	22,236,168	2,965	7,500
	20% increase	22,237,416	4,490	4,953
Utility decrement for each clinical event	20% decrease	22,239,621	3,676	6,050
	20% increase	22,234,438	3,765	5,906

BCV = best cut-off value; HR = hazard ratio; ICUR = incremental cost-utility ratio; MI = myocardial infarction; PAD = peripheral artery disease; QALY = quality-adjusted life-years.

[a] In this sensitivity analysis, the baseline HRs for modelled clinical events were varied by ± 10% (0.90 and 1.10). [1]

[b] In this sensitivity analysis, the patient utility at baseline (0.785) was varied by ± 20%.[1]

Source: Manufacturer's pharmacoeconomic report, table 10, page 12.[1]

Manufacturer's Scenario Analysis: Exploration of Long-Term Post-Event Costs

Inclusion of long-term costs for clinical events has the potential to double-count costs; therefore, long-term costs were not included in the base case. The manufacturer conducted a scenario analysis by including long-term costs (comprising those relating to events before entry into the model and those incurred due to events occurring after entry into the model).[1] In this analysis, the ICUR increased slightly to $10,341 per QALY. This result is primarily driven by the longer lifespan of patients in the empagliflozin group, who incur additional long-term costs (total costs per patient were $3,251 higher in the

empagliflozin group than in the standard care group). When the treatment effect of empagliflozin was removed after the first event, the ICUR fell slightly to $4,708 per QALY, driven primarily by a reduction in survival benefit compared with the base case.

The manufacturer also conducted additional scenario analyses in which all long-term costs were set to zero except for stroke and renal failure. This addressed the concern that for stroke and renal failure, the majority of long-term costs are not driven by repeat events, but by nursing care due to disability (for stroke) and dialysis (for renal failure). The ICUR was $8,209 per QALY.

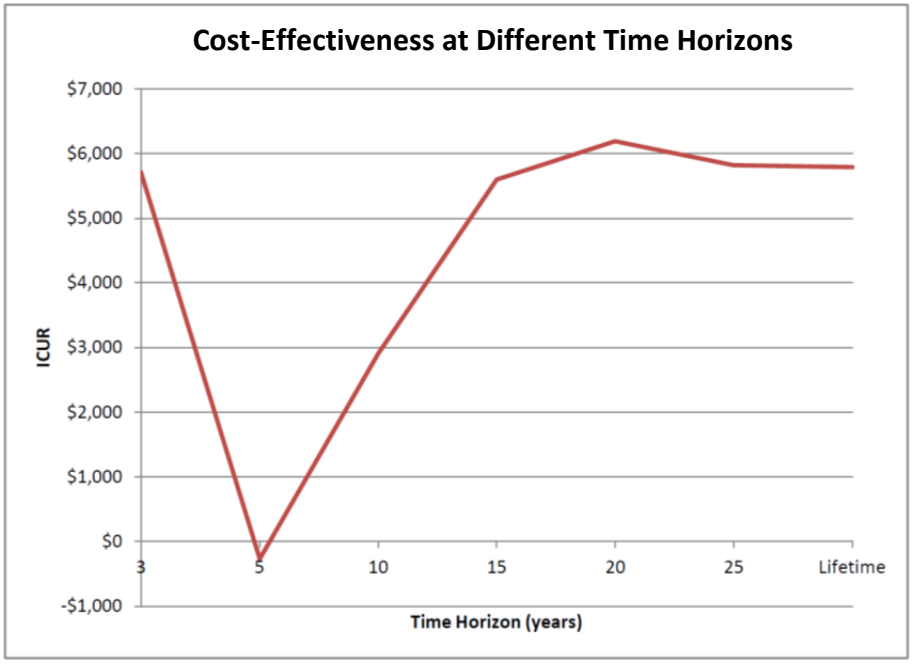
Manufacturer's Scenario Analysis: Utility Values From CADTH Therapeutic Reviews

A scenario analysis was conducted based on the disutility values from the CADTH Therapeutic Reviews on antidiabetic therapy.[9] The ICUR increased from $5,977 per QALY to $6,072 per QALY.

Manufacturer's Scenario Analysis: Time Horizon

The manufacturer conducted analyses over a number of time periods, ranging from three years (trial duration) up to and including a lifetime time horizon. Ten thousand simulations were used in this analysis rather than 5,000 simulations as in the base case, due to the higher number of simulations required to achieve convergence at shorter time periods. The results are presented in Figure 3. Overall, cost-effectiveness results were consistent with the base-case analysis for most time horizons. The only exception was at five years, where empagliflozin appeared to be dominant over standard care; the reason for this divergence from the results for other time horizons was unclear, but it may be related to the selected distributions used to extrapolate long-term event rates.

FIGURE 3: COST-EFFECTIVENESS RESULTS AT DIFFERENT TIME HORIZONS USING THE MANUFACTURER'S BASE-CASE MODEL (10,000 PATIENTS)

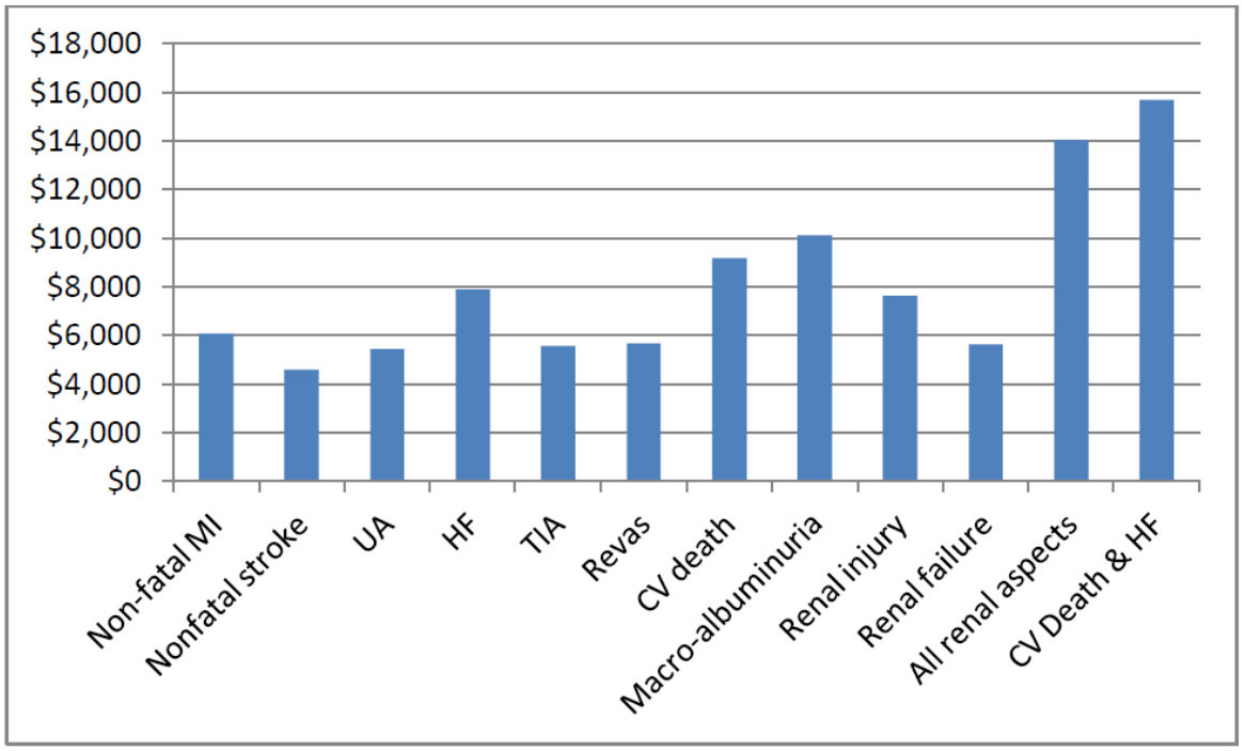


ICUR = incremental cost-utility ratio.
Source: Manufacturer's pharmacoeconomic submission.[1]

Manufacturer's Scenario Analysis: Treatment Effect of Empagliflozin

The manufacturer conducted a series of analyses where the treatment effect of empagliflozin was removed. In the first series, where the effect of empagliflozin was removed for every event after the first event, the results showed that the number of life-years gained was reduced to 0.6, with incremental QALYs reduced to 0.26. The incremental event cost was also reduced to $2,016, while the drug cost remained the same. This resulted in an ICUR of $24,201 per QALY. In the second series, where the treatment effect of empagliflozin on each type of event individually was removed, the ICUR appeared to be in a range that would be considered cost-effective across all analyses (
Figure 4).

FIGURE 4: ICUR RESULTS UPON REMOVAL OF TREATMENT EFFECT OF EMPAGLIFLOZIN ON INDIVIDUAL CLINICAL EVENTS



CV = cardiovascular; HF = heart failure; ICUR = incremental cost-utility ratio; TIA = transient ischemic attack; UA = unstable angina.
Source: Manufacturer's pharmacoeconomic submission.[1]

Manufacturer's Scenario Analysis: Probabilistic Sensitivity Analyses

A probabilistic sensitivity analysis (PSA) was run using 500 replications of 1,000 patients each. The manufacturer noted that using a smaller number of patients per replication tended to increase the variance in the PSA.[1] The PSA found relatively broad 95% confidence intervals (CIs) around the event rates for both the empagliflozin and standard care groups. The cost-effectiveness acceptability curve (CEAC) showed a 99.6% probability of being cost-effective at a willingness-to-pay of $50,000.

REFERENCES

1. Pharmacoeconomic evaluation. In: CDR submission: Jardiance (empagliflozin), 10 mg and 25 mg tablets. Company: Boehringer Ingelheim (Canada) Ltd [**CONFIDENTIAL** manufacturer's submission]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd; 2016 Apr 27.
2. Jardiance™ (empagliflozin tablets): 10 mg and 25 mg tablets [product monograph]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd; 2016 Aug 10.
3. Common Drug Review. CADTH CDEC final recommendation: empaglifozin (Jardiance - Boehringer Ingelheim (Canada) Ltd.). Indication: type 2 diabetes mellitus [Internet]. Ottawa: CADTH; 2015 Oct 15. [cited 2016 Jun 23]. Available from: https://www.cadth.ca/sites/default/files/cdr/complete/sr0427_jardiance_oct-19-15.pdf
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015 Nov 26 [cited 2016 May 13];373(22):2117-28.
5. Goeree R, Lim ME, Hopkins R, Blackhouse G, Tarride JE, Xie F. Prevalence, total and excess costs of diabetes and related complications in Ontario, Canada. Can J Diabetes. 2009;33(1):35-45.
6. Smolderen KG, Bell A, Lei Y, Cohen EA, Steg PG, Bhatt DL, et al. One-year costs associated with cardiovascular disease in Canada: Insights from the REduction of Atherothrombosis for Continued Health (REACH) registry. Can J Cardiol [Internet]. 2010 Oct [cited 2016 Aug 25];26(8):297-305. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2954538
7. Sullivan PW, Ghushchyan VH. EQ-5D scores for diabetes-related comorbidities. Value Health. Forthcoming 2016.
8. Barry HC, Ebell MH, Hickner J. Evaluation of suspected urinary tract infection in ambulatory women: A cost-utility analysis of office-based strategies. J Fam Pract. 1997 Jan;44(1):49-60.
9. Third-line pharmacotherapy for type 2 diabetes - update [Internet]. Ottawa: CADTH; 2016. [cited 2016 Jun 17]. (CADTH optimal use report, volume 3, issue 1B). Available from: https://www.cadth.ca/media/pdf/OP0512_Diabetes%20Update_Third-line_e.pdf
10. Régie de l'assurance maladie Québec. Liste des médicaments [Internet]. Québec (QC): Gouvernement du Québec; 2016. [cited 2016 Jun 17]. Available from: http://www.ramq.gouv.qc.ca/fr/regie/publications-legales/Pages/liste-medicaments.aspx
11. Interactive drug benefit list [Internet]. [Edmonton]: Alberta Health; 2016. [cited 2016 Jun 17]. Available from: https://www.ab.bluecross.ca/dbl/idbl_main1.html
12. DeltaPA [database on Internet]. Ottawa: QuintilesIMS; 2016. [cited 2016 Jun 17]. Available from: http://www.imsbrogancapabilities.com/en/market-insights/delta-pa.html
13. Drug Plan and Extended Benefits Branch. Saskatchewan online formulary database [Internet]. Regina: Government of Saskatchewan; 2016. [cited 2016 Jun 20]. Available from: http://formulary.drugplan.health.gov.sk.ca/
14. Drugs funded by Ontario Drug Benefit (ODB) Program. E-formulary [Internet]. Toronto: Ontario Ministry of Health and Long-Term Care; 2016. [cited 2016 Jun 17]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/odbf_eformulary.aspx