Common Drug Review
Pharmacoeconomic Review Report

September 2015

Drug	canagliflozin (Invokana)
Indications	Indicated in combination with metformin and either a sulfonylurea or pioglitazone in adult patients with type 2 diabetes mellitus to improve glycemic control when diet, exercise, and dual therapy (with metformin plus either a sulfonylurea or pioglitazone) do not provide adequate glycemic control.
Listing request	List as third-line therapy added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea.
Manufacturer	Janssen Inc.

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ABBREVIATIONS

A1C	glycated hemoglobin
AE	adverse event
BMI	body mass index
CDR	CADTH Common Drug Review
CKD	chronic kidney disease
DPP-4	dipeptidyl peptidase-4
ESRD	end-stage renal disease
ECHO-T2DM	Economics and Health Outcomes Model for type 2 diabetes mellitus
eGFR	estimated glomerular filtration rate
GLP-1	glucagon-like peptide-1
GMI	genital mycotic infection
NMA	network meta-analysis
NPH	neutral protamine Hagedorn
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SBP	systolic blood pressure
SGLT2	sodium-glucose cotransporter-2
T2DM	type 2 diabetes mellitus
TZD	thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study
UKPDS-OM2	United Kingdom Prospective Diabetes Study Outcomes Model 2
UTI	urinary tract infection

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Canagliflozin 100 mg and 300 mg tablets
Study Question	To evaluate the cost-effectiveness of canagliflozin 100 mg and 300 mg tablets versus sitagliptin 100 mg as third-line therapy in adults aged 18 years and older with T2DM in the Canadian setting. • In patients who are inadequately controlled on metformin plus a sulfonylurea alone (manufacturer's listing request) • In patients who are inadequately controlled on metformin plus pioglitazone therapy alone
Type of Economic Evaluation	Cost-utility analysis
Target Population	Patients with T2DM who have inadequate glycemic control on: • metformin plus a sulfonylurea (base case 1) • metformin plus pioglitazone (base case 2)
Treatment	Canagliflozin 100 mg once daily and 300 mg once daily as add-on to metformin plus a sulfonylurea or metformin plus pioglitazone
Outcome	Quality-adjusted life-years
Comparators	Sitagliptin 100 mg once daily as add-on to metformin plus a sulfonylurea, or metformin plus pioglitazone
Perspective	Ministry of health
Time Horizon	Lifetime (up to 40 years)
Results for Base Case	• Canagliflozin (300 mg or 100 mg) vs. sitagliptin 100 mg added to metformin plus a sulfonylurea: Canagliflozin is dominant — associated with greater health gains and lower total costs • Canagliflozin (300 mg or 100 mg) vs. sitagliptin 100 mg added to metformin plus pioglitazone: Canagliflozin is dominant — associated with greater health gains and lower total costs
Key Limitations	CDR noted a number of limitations with the manufacturer's model: • Lack of consideration of variability in the pricing of DPP-4 inhibitors across CDR-participating drug plans • Other third-line treatments (insulin, GLP-1 agonists) were not considered as comparators in the analysis • In the absence of head-to-head trials comparing canagliflozin 100 mg and sitagliptin 100 mg, many clinical inputs were taken from the intervention group of the trials for each individual comparator, thus creating an unadjusted indirect comparison • Heterogeneity among the trials included in the NMA used to elicit treatment effects for canagliflozin 100 mg • Lower disutility value associated with weight gain has been reported in the literature • Hypoglycemia rates in the sitagliptin group for the canagliflozin 100 mg vs. sitagliptin 100 mg comparison might have been overestimated

CDR Estimate(s)	CDR performed a number of reanalyses in the population inadequately controlled on metformin plus a sulfonylurea to assess the impact of some of the parameter uncertainties:
	• All reanalyses showed canagliflozin 300 mg and 100 mg to be dominant over sitagliptin 100 mg (using a price of $2.62 daily for sitagliptin 100 mg)
	• CDR reanalyses on canagliflozin 100 mg, using a lower price for sitagliptin 100 mg of $2.25 daily (lowest list price of a DPP4-inhibitor), in addition to:
	  • Similar rate of severe hypoglycemic events for sitagliptin and canagliflozin 100 mg (ICUR: $23,280 per QALY)
	  • Higher rate of discontinuation of sitagliptin due to adverse events based on one-year data from the DIA3015 trial (ICUR: $16,421 per QALY)
	  • Lower increase in systolic blood pressure for sitagliptin using lower bound of credible interval from the NMA (ICUR: $18,057 per QALY)
	  • Lower increase in BMI for sitagliptin, using lower bound of credible interval from the NMA (ICUR: $22,440 per QALY)
	  • Disutility associated with weight gain from the CADTH Optimal Use Report on third-line pharmacotherapy for patients with T2DM (ICUR: $35,150 per QALY)

BMI = body mass index; CDR = CADTH Common Drug Review; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year; T2DM = type 2 diabetes mellitus; vs = versus.

EXECUTIVE SUMMARY

Background

Canagliflozin (Invokana) is the first antihyperglycemic drug of the sodium-glucose cotransporter-2 (SGLT2) inhibitor class indicated for use in Canada. This CADTH Common Drug Review (CDR) report will focus on the following indication:

> In combination with metformin and either a sulfonylurea or pioglitazone in adult patients with type 2 diabetes mellitus to improve glycemic control when diet, exercise, and dual therapy (with metformin plus either a sulfonylurea or pioglitazone) do not provide adequate glycemic control.

The recommended starting dose of canagliflozin is 100 mg once daily. In patients tolerating canagliflozin 100 mg once daily who need tighter glycemic control, the 300 mg dose may be considered for patients if they have an estimated glomerular filtration rate (eGFR) of ≥ 60 mL/min/1.73 m^2 and have a low risk of adverse reactions associated with reduced intravascular volume due to canagliflozin treatment.[1] The manufacturer submitted a flat price of $2.6177 per 100 mg or 300 mg tablet ($2.62 daily).

The manufacturer submitted a cost-utility analysis comparing canagliflozin 100 mg and canagliflozin 300 mg to sitagliptin 100 mg as add-on to metformin plus a sulfonylurea (base case 1), or metformin plus pioglitazone (base case 2). The effectiveness of canagliflozin 300 mg was compared with sitagliptin 100 mg using data from the active-comparator randomized controlled trial (DIA3015).[2-4] In the absence of head-to-head trial data for the canagliflozin 100 mg and sitagliptin 100 mg comparison, a network meta-analysis was used for some outcomes (change in glycated hemoglobin, change in systolic blood pressure, change in body mass index), but many clinical inputs were taken from the intervention group of the pivotal trials for each individual comparator (unadjusted indirect comparison). The time horizon was the patient's lifetime (up to 40 years) using the Canadian public payer perspective. The economic analyses were carried out using the Economics and Health Outcomes Model for type 2 diabetes mellitus.

The manufacturer's base-case results show canagliflozin (100 mg and 300 mg) to dominate sitagliptin 100 mg: canagliflozin results in more benefit at a lower cost than sitagliptin both in patients inadequately controlled on metformin plus a sulfonylurea, and those on metformin plus pioglitazone. Sensitivity analyses conducted by the manufacturer indicated the base-case results are robust.

Summary of Identified Limitations and Key Results

- Comparators did not include all available third-line treatments and did not account for variation in pricing of dipeptidyl peptidase-4 (DPP-4) inhibitors across drug plans.
- Treatment effects for canagliflozin 100 mg were derived from a network meta-analysis as well as from the intervention group of the pivotal trials for each individual comparator. Use of more conservative estimates for comparative treatment effects did not change overall results.
- Lower disutility value associated with weight gain has been reported in the literature.[5,6]
- Hypoglycemia rates in the sitagliptin group might have been overestimated.

The manufacturer's base-case comparison was for canagliflozin (300 mg and 100 mg) as a third-line drug added on to metformin plus a sulfonylurea, or metformin plus pioglitazone background; however, based on discussion with the clinical expert for this review, it was determined that patients with a metformin plus pioglitazone background constitute a minority among type 2 diabetes mellitus patients in Canada,

due to the risk of congestive heart failure in patients using thiazolidinediones.[6] Therefore, CDR reanalyses focused on canagliflozin being added on to metformin plus a sulfonylurea background, which was also consistent with the approach taken for the CDR clinical review.

Results of CDR one-way sensitivity analyses on glycated hemoglobin, systolic blood pressure, body mass index, severe hypoglycemic events, and discontinuation rates at the manufacturer-submitted price for canagliflozin ($2.62 daily) indicate that the results are robust (i.e., canagliflozin 300 mg and 100 mg still dominate sitagliptin 100 mg). Due to variability in DPP-4 inhibitor reimbursement across Canada, the CDR used a lower price for sitagliptin of $2.25 daily, which is the lowest list cost for a DPP-4 inhibitor (Nova Scotia public drug formulary, September 2014).[7] The results of the one-way sensitivity analyses using the lower price show that the incremental cost-utility ratio for canagliflozin (300 mg and 100 mg) ranges from being dominant to $35,150 per quality-adjusted life-year.

Conclusions

As a third-line treatment added on to metformin plus a sulfonylurea or metformin plus pioglitazone, the manufacturer suggests that canagliflozin 100 mg and 300 mg dominate sitagliptin 100 mg, based on assumptions of clinical benefit and similar pricing over a lifetime time horizon. The manufacturer's analysis did not include a comparison with other third-line treatments. Using a lower price for sitagliptin (based on the lowest list price for a DPP-4 inhibitor in participating drug plans), CDR reanalyses showed that the incremental cost-utility ratio for canagliflozin (300 mg and 100 mg) compared with sitagliptin 100 mg, ranges from being dominant to $35,150 per quality-adjusted life-year.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis comparing canagliflozin 100 mg and 300 mg to sitagliptin 100 mg as third-line drug added to a combination of metformin plus a sulfonylurea, or metformin plus pioglitazone. The effectiveness of canagliflozin 300 mg was compared with sitagliptin 100 mg using data from the active-comparator randomized controlled trial (DIA3015).[2,4] For the canagliflozin 100 mg and sitagliptin 100 mg comparison, a network meta-analysis (NMA) was used to populate the analyses in the absence of head-to-head trial data.[8] The reference-case time horizon was the patient's lifetime (up to 40 years) using the Canadian public payer perspective. The economic analyses were carried out using the Economics and Health Outcomes Model for type 2 diabetes mellitus (ECHO-T2DM).

ECHO-T2DM is a validated and complex patient-level micro-simulation model that generates cohorts of hypothetical patients defined by a set of characteristics, including demographics (e.g., age and gender), bio-marker values (e.g., glycated hemoglobin [A1C], systolic blood pressure [SBP], and body mass index [BMI]), and disease indicators (e.g., disease duration and history of microvascular and macrovascular complications).[9] The characteristics of these cohorts are sourced primarily from the baseline characteristics observed in randomized controlled trials (RCTs). The ECHO-T2DM model allows the use of the recent United Kingdom Prospective Diabetes Study (UKPDS) macrovascular and mortality risk equations from the UKPDS Outcomes Model 2.[10] The ECHO-T2DM simulates the progression of intermediary outcomes associated with microvascular complications such as microalbuminuria, foot ulceration, and diabetic neuropathy, in addition to end-stage culminations like end-stage renal disease (ESRD), blindness, and amputation. The ECHO-T2DM allows the capture of differences in the costs and disutility at the relatively more common sub–end-stage level. The ECHO-T2DM also features a full chronic kidney disease (CKD) module based on the Centers for Disease Control and Prevention Model of CKD, featuring actual kidney functioning as well as kidney disease.[11]

The disutility weights associated with complications of type 2 diabetes mellitus were primarily sourced from the CADTH Optimal Use Report on third-line pharmacotherapy for patients with type 2 diabetes mellitus.[6] Where suitable estimates were lacking, such as was the case for utility decrements associated with modelled treatment-related adverse events and excess weight, data were supplemented from the literature.[12-14] The manufacturer conducted a time–trade-off (TTO) study to estimate utility values for selected health states, including gender-specific genital mycotic infections (GMIs).[15] The disutility associated with excess weight was obtained from Bagust and Beale 2005.[16]

Unit costs for drugs were obtained from the Ontario Drug Benefit Formulary (2013);[17] otherwise, prices were obtained from the Quebec public plan, including the price of sitagliptin (2013).[18] For the base case, it was assumed that episodes of symptomatic non-severe hypoglycemia had no impact on the use of health service resources. Resource utilization associated with managing severe hypoglycemic episodes was derived from the same sources used for the CADTH Optimal Use Report on third-line pharmacotherapy for patients with type 2 diabetes mellitus.[6] Costs associated with long-term management of diabetes-related complications were obtained from several sources.[6,19-21]

2. MANUFACTURER'S BASE CASE

In the first reference case (i.e., third-line therapy added to metformin plus a sulfonylurea), the manufacturer reported that canagliflozin 100 mg and canagliflozin 300 mg resulted in mean increases in quality-adjusted life-years (QALYs) of 0.04 and 0.08, respectively and, over 40 years, were associated with lower costs of $981 and $2,035, respectively, compared with sitagliptin 100 mg.

In third-line therapy with metformin plus pioglitazone, treatment with canagliflozin 300 mg and canagliflozin 100 mg resulted, respectively, in a mean increase in QALYs of 0.08 and 0.05, and was associated with lower costs of $683 and $492 over 40 years, compared with sitagliptin 100 mg.

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

Base-Case Scenario	Incremental Cost ($)	Incremental QALY	Incremental LY	ICUR of Canagliflozin Versus Sitagliptin
Third-line therapy: metformin plus a sulfonylurea background				
1a) Canagliflozin 300 mg	–$2,035	+0.08	+0.05	Canagliflozin is dominant
1b) Canagliflozin 100 mg	–$981	+0.04	+0.02	
Third-line therapy: metformin plus pioglitazone background				
2a) Canagliflozin 300 mg	–$683	+0.08	+0.03	Canagliflozin is dominant
2b) Canagliflozin 100 mg	–$492	+0.05	+0.02	

ICUR = incremental cost-utility ratio; LY = life-years; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer's pharmacoeconomic submission, page 22, Table 8.11.[11]

In the metformin plus a sulfonylurea reference-case scenario, canagliflozin 300 mg and 100 mg were associated with an increase in life-years of 0.05 and 0.02, respectively, compared with sitagliptin 100 mg. In the metformin plus pioglitazone reference scenario, the increase in life-years was 0.03 and 0.02 for canagliflozin 300 mg and 100 mg, respectively, compared with sitagliptin 100 mg.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Uncertainty was addressed using one-way deterministic sensitivity analyses that varied model parameters by using alternative values. The results indicate that canagliflozin 300 mg remained the least costly and most effective option in combination with metformin plus a sulfonylurea, or metformin plus pioglitazone. Canagliflozin 100 mg showed similar dominance in all sensitivity analyses of interest (discount rates, time horizons, A1C thresholds, and disutility weights around weight gain). It was only in the scenario of canagliflozin 100 mg with metformin plus pioglitazone that an incremental cost-utility ratio was observed for $365 per QALY when the time horizon was reduced to five years.

In addition, the manufacturer conducted scenario analyses on dose escalation of canagliflozin. The manufacturer also conducted sensitivity analyses addressing the use of canagliflozin as second-line therapy to correspond with the use of sitagliptin as second-line therapy in Ontario and Quebec. Results show canagliflozin 100 mg and 300 mg dominate sitagliptin 100 mg both as second-line therapy and when doses are increased in third-line therapy (Table 3).

TABLE 3: SUMMARY OF RESULTS OF THE MANUFACTURER'S SCENARIO ANALYSES

	Incremental Cost	Incremental QALYs	ICUR
Dose increase in third-line therapy sensitivity analysis			
Canagliflozin 100 mg or 300 mg vs. sitagliptin 100 mg (metformin plus a sulfonylurea)[a]	–$1,062	0.06	Dominant
Canagliflozin 100 mg or 300 mg vs. sitagliptin 100 mg (metformin plus pioglitazone)[b]	–$925	0.06	Dominant
Second-line therapy sensitivity analysis (plus metformin)[c]			
Canagliflozin 300 mg vs. sitagliptin 100 mg	–$1,317	0.07	Dominant
Canagliflozin 100 mg vs. sitagliptin 100 mg	–$800	0.04	Dominant

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs = versus.
Source: Adapted from manufacturer's pharmacoeconomic submission, page 34, Tables 8.14 and 8.15.[11]
[a] Patient-level data from clinical trial DIA3012 and network meta-analysis for efficacy and adverse events.[22]
[b] Patient-level data from clinical trial DIA3002 and network meta-analysis for efficacy and adverse events.[23]
[c] Patient-level data on efficacy and adverse events from clinical trial DIA3006.[11]

3.1 Probabilistic Sensitivity Analysis

The cost-effectiveness acceptability curves indicate that canagliflozin 100 mg and 300 mg have high likelihoods of being cost-effective versus sitagliptin 100 mg at all levels of willingness-to-pay for an additional QALY for both base cases (metformin plus a sulfonylurea, and metformin plus pioglitazone). For base case 1, with no willingness-to-pay for a QALY (i.e., at the origin of $0), canagliflozin 300 mg and 100 mg are nearly 100% and 60% likely to be cost-effective, respectively. For base case 2, with no willingness-to-pay for a QALY (i.e., at the origin of $0), canagliflozin 300 mg and 100 mg are almost 75% and 70% likely to be cost-effective, respectively.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

4.1 Variability in the Pricing of DPP-4 Inhibitors

The manufacturer selected dipeptidyl peptidase-4 (DPP-4) inhibitors as the comparator class for canagliflozin 300 mg and 100 mg based on the CADTH Optimal Use Report on third-line pharmacotherapy for patients with type 2 diabetes mellitus,[6] which indicated that DPP-4 inhibitors are the most cost-effective option under certain assumptions, including insulin not being an option. Based on prescription data, sitagliptin was suggested to be the most frequently used DPP-4 inhibitor for type 2 diabetes in Canada and, therefore, canagliflozin 300 mg and 100 mg were priced based on the lowest publicly listed price of sitagliptin 100 mg in Canada (Quebec).[11] However, consistent with the CADTH review on therapies for type 2 diabetes mellitus, an analysis using the price of the lowest DPP-4 inhibitor would have been relevant.

4.2 Choice of Comparators

The manufacturer's submitted base-case analysis compared canagliflozin to sitagliptin as a third-line drug added on to metformin plus a sulfonylurea, or metformin plus pioglitazone. Other third-line treatments are available in Canada but were not included in the analysis, such as glucagon-like peptide-1 agonists and insulin. Although justification was provided for the choice of sitagliptin as comparator, the manufacturer did not provide the reasons for excluding glucagon-like peptide-1 and insulin.

4.3 Unadjusted Indirect Comparison for Many Outcomes for the Canagliflozin 100 mg and Sitagliptin 100 mg Comparison

In the absence of head-to-head trials comparing canagliflozin 100 mg and sitagliptin 100 mg, many clinical inputs (e.g., cholesterol, triglycerides, GMIs, UTIs) were taken from the intervention group of the trials for each individual comparator, thus creating an unadjusted indirect comparison.

4.4 Limitations With the Network Meta-analysis for Canagliflozin 100 mg and Sitagliptin 100 mg Comparison

The manufacturer conducted a Bayesian NMA analysis based on a systematic review of RCTs that compared canagliflozin (100 mg or 300 mg) with other antidiabetic drugs. The results of the NMA were used to inform the treatment effects of canagliflozin 100 mg versus sitagliptin on A1C, SBP, and BMI. Potential limitations of the NMA were the heterogeneity in terms of the variable trial duration and baseline A1C; the methodological quality of the individual studies; the definition of hypoglycemia; etc. However, the results of various sensitivity analyses that excluded some specific RCTs showed no or minimal impact on the findings of the base-case analysis; therefore, it is unlikely that the heterogeneity had a significant clinical impact on the overall NMA findings. In addition, it is unclear whether all potentially eligible studies (such as a study on saxagliptin[24]) were included.

4.5 Disutility Value Associated With Weight Gain

The manufacturer applied a utility reduction of 0.0061 for every 1 kg/m^2 increase above a BMI of 25, based on Bagust and Beale (2005).[16] A lower disutility value (0.001950) has been used in the literature.[5,6]

4.6 Estimation of Hypoglycemia Rates With Sitagliptin

Data on severe and non-severe hypoglycemia event rates for the canagliflozin 100 mg group were sourced from the DIA3002[11] trial. The event rates for sitagliptin were estimated by multiplying the canagliflozin 100 mg rates and the odds ratio for the proportion of patients experiencing hypoglycemia events as estimated in the NMA. The model assumed a greater rate of hypoglycemic events with sitagliptin, while the NMA showed no difference in the odds ratio between canagliflozin 100 mg and sitagliptin 100 mg (odds ratio 0.75; 95% CrI, 0.43 to 1.29) for all hypoglycemic events.[8]

5. CADTH COMMON DRUG REVIEW ANALYSES

The manufacturer's base-case comparison was for canagliflozin (300 mg and 100 mg) as a third-line therapy added on to metformin plus a sulfonylurea, or metformin plus pioglitazone background. However, based on discussion with the clinical expert on this review, it was determined that patients with a metformin plus pioglitazone background constitute a small minority among type 2 diabetes mellitus patients in Canada due to the risk of congestive heart failure in patients using thiazolidinediones.[6] Therefore, CDR reanalyses will be focused on canagliflozin being added on to a metformin plus a sulfonylurea background.

Based on the variability of sources used by the manufacturer in obtaining the effect estimates for canagliflozin 100 mg, and conflicting results between the manufacturer's estimates of the rates of hypoglycemic events compared with the NMA findings, CDR conducted one-way sensitivity analyses on several parameters (A1C, SBP, BMI, hypoglycemic events, treatment discontinuation rate, and disutility with weight gain) to assess the robustness of the manufacturer's results.

Given the variability in reimbursement costs for DPP-4 inhibitors paid by public drug plans in Canada, and consistent with the CADTH review on therapies for type 2 diabetes that used the price of the lowest cost alternative for each drug class, the one-way sensitivity analyses were conducted using both the manufacturer's submitted price for sitagliptin ($2.6177 per 100 mg tablet, based on the list price of the Quebec public plan), and the lowest price for a DPP-4 inhibitor covered by a public drug plan ($2.25 per 5 mg tablet of linagliptin, Nova Scotia formulary).[7] The summary results are presented in Table 4.

TABLE 4: SUMMARY OF RESULTS OF THE CADTH COMMON DRUG REVIEW REANALYSES

	ICUR ($/QALY)	
	Base-Case Price of Sitagliptin 100 mg of $2.6177[a]	Reduced Price of Sitagliptin 100 mg to $2.25[b]
Lower price only (using lowest price of DPP-4 inhibitor in Canada)[b]	NA	$15,558
Similar effect on A1C	Dominating	$2,563
Lower bound of 95% credible interval for sitagliptin effect on SBP (0.28)[c]	Dominating	$18,057
Lower bound of 95% credible interval for sitagliptin effect on BMI (–0.01)[c]	Dominating	$22,440
Event rate for severe hypoglycemia for sitagliptin (0.014)	Dominating	$23,280
Discontinuation rate for sitagliptin due to adverse events (0.037)	Dominating	$16,421
Lower disutility value for weight gain (0.001950)[d]	Dominating	$35,150
Canagliflozin 300 mg	NA	Dominating

A1C = glycated hemoglobin; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4 inhibitor; NA = not applicable; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SBP = systolic blood pressure.

[a] Quebec list price for sitagliptin.

[b] Price of 5 mg tablet of linagliptin as listed on Nova Scotia public drug plan (September 2014).[7]

[c] Results from the manufacturer-submitted network meta-analysis.[8]

[d] This is the value that was used in the CADTH report[6] and was sourced from the National Institute for Health and Care Excellence.[5]

6. PATIENT INPUT

The availability of canagliflozin as an alternative treatment option for stabilizing blood glucose was reported as important to patients. Patient input also described lowering of blood pressure to be important and essential. These two outcomes and their impact on costs and quality of life were included in the economic model.

7. CONCLUSIONS

As a third-line treatment added to metformin plus a sulfonylurea, or metformin plus pioglitazone, the manufacturer suggests that canagliflozin 100 mg and 300 mg dominate sitagliptin 100 mg, based on assumptions of clinical benefit and similar pricing over a lifetime time horizon. The manufacturer's analysis did not include a comparison with other third-line treatments. Using a lower price for sitagliptin based on the lowest list price in participating drug plans for a DPP-4 inhibitor, CDR reanalyses showed that the incremental cost-utility ratio for canagliflozin (300 mg and 100 mg) compared with sitagliptin 100 mg ranges from being dominant to $35,150 per QALY.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 5 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 5: COST-COMPARISON TABLE FOR SODIUM-GLUCOSE COTRANSPORTER-2 AND DIPEPTIDYL PEPTIDASE-4 INHIBITORS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Subtype 2 sodium-glucose cotransporter protein inhibitors						
Canagliflozin (Invokana)	100 mg 300 mg	Tablet	2.6177[a]	100 or 300 mg once daily	2.62	955
Dipeptidyl peptidase-4 inhibitors						
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	Tablet	2.8403[b]	25 mg daily	2.62	955
Linagliptin (Trajenta)	5 mg	Tablet	2.5500[c]	5 mg daily	2.55	931
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	Tablet	2.3690 2.8387	5 mg daily	2.84	1,036
Sitagliptin (Januvia)	100 mg	Tablet	2.9527	100 mg daily	2.95	1,078

[a] Manufacturer's submission price.
[b] McKesson Canada wholesale price (October 2014); includes markup.[25]
[c] Variability in price exists across provinces; linagliptin is listed at $2.25 per 5 mg tablet on Nova Scotia drug formulary.[7]
Source: Ontario Drug Benefit Formulary (October 2014) prices, unless otherwise indicated.[17]

TABLE 6: COST-COMPARISON TABLE FOR OTHER NON-INSULIN ANTIDIABETES DRUGS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
DPP-4 plus metformin fixed-dose combinations						
Alogliptin/ metformin (Kazano)	12.5/500 mg 12.5/850 mg 12.5/1,000 mg	Tablet	1.4865[a]	Two tablets daily	2.74	1,000
Linagliptin/ metformin (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	Tablet	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	Tablet	1.3716[b]	Two tablets daily	2.76	1,006
Sitagliptin/ metformin (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	Tablet	1.6015	Two tablets daily	3.20	1,169
Biguanides						
Metformin	500 mg 850 mg	Tablet	0.0587 0.1186[c]	500 mg three to four times daily	0.18 to 0.23	64 to 86
Glucagon-like peptide-1 receptor agonist						
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/mL)	149.4100[a]	10 mcg twice daily	4.98	1,817
Liraglutide (Victoza)	2 x 3 mL 3 x 3 mL	Pre-filled pen (6 mg/mL)	175.1900[a] 262.7800[a]	1.2 mg to 1.8 mg daily	5.84 to 8.76	2,131 to 3,197
Insulin secretagogues, sulfonylureas						
Gliclazide (generics)	80 mg	Tablet	0.0931	80 to 320 mg daily (in divided doses if > 160 mg daily)	0.09 to 0.37	34 to 136
Gliclazide long-acting (Diamicron MR)	30 mg 60 mg	ER tablet	0.1405 0.2529	30 mg to 120 mg daily	0.14 to 0.51	51 to 185
Glimepiride (generics)	1 mg 2 mg 4 mg	Tablet	0.4851[d]	1 mg to 4 mg daily	0.49	177
Glyburide (generics)	2.5 mg 5.0 mg	Tablet	0.0321 0.0574	2.5 mg to 20 mg daily (in divided doses if > 10 mg daily)	0.03 to 0.23	12 to 84
Thiazolidinediones						
Pioglitazone (generics)	15 mg 30 mg 45 mg	Tablet	0.8133[c] 1.1394[c] 1.7132[c]	15 mg to 45 mg daily	0.81 to 1.71	267 to 625

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Rosiglitazone (Avandia)	2 mg 4 mg 8 mg	Tablet	1.3755[c] 2.1584[c] 3.0865[c]	4 to 8 mg daily	2.16 to 3.09	788 to 1,126
Rosiglitazone/ metformin (Avandamet)	1/500 mg 2/500 mg 4/500 mg 2/1,000 mg 4/1,000 mg	Tablet	0.6421[c] 1.1611[c] 1.5943[c] 1.2682[c] 1.7337[c]	4/1,000 to 8/2,000 mg daily in divided doses	2.32 to 3.47	847 to 1,266
Alpha-glucosidase inhibitors						
Acarbose (Glucobay)	50 mg 100 mg	Tablet	0.2682 0.3714	50 to 100 mg 3 times daily	0.80 to 1.11	294 to 407

DPP-4 = dipeptidyl peptidase-4; ER = extended release; MR = modified release.
[a] McKesson Canada wholesale price (Aug 2014).[25]
[b] BC drug formulary (October 2014).[26]
[c] Saskatchewan drug formulary (October 2014).[27]
[d] Manitoba drug formulary (October 2014).[28]
Source: Ontario Drug Benefit Formulary (October 2014) prices unless otherwise indicated.[17]

TABLE 7: COST-COMPARISON TABLE FOR BASAL INSULINS

Drug/Comparator	Strength	Dosage Form	Price ($)	Cost per mL ($)
Intermediate-acting human insulin				
Humulin N	100 U/mL	5 × 3 mL cartridge 10 mL vial	44.24 22.54	2.95 2.25
Novolin ge NPH	100 U/mL	5 × 3 mL cartridge 10 mL vial	42.23 21.49	2.82 2.15
Long-acting insulin analogues				
Insulin glargine (Lantus)	100 U/mL	5 × 3 mL cartridge 5 × 3 disposable pen 10 mL vial	92.20 92.20 61.06	6.15 6.15 6.11
Insulin detemir (Levemir)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	101.68 106.76	6.78 7.12

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS CANAGLIFLOZIN 300 MG RELATIVE TO SITAGLIPTIN?

Canagliflozin 300 mg versus Sitagliptin	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)	X					
Drug treatment costs alone	X					
Clinical outcomes		X				
Quality of life		X				
ICER or net benefit calculation	Canagliflozin dominates sitagliptin					

ICER = incremental cost-effectiveness ratio; NA = not applicable.
Note: Based on manufacturer's results.

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS CANAGLIFLOZIN 100 MG RELATIVE TO SITAGLIPTIN?

Canagliflozin 100 mg versus Sitagliptin	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)	X					
Drug treatment costs alone	X					
Clinical outcomes		X				
Quality of life		X				
ICER or net benefit calculation	Canagliflozin dominates sitagliptin					

ICER = incremental cost-effectiveness ratio; NA = not applicable.
Note: Based on manufacturer's results.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 10: 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 11: AUTHOR INFORMATION

Authors	Affiliations		
None specified	The Swedish Institute For Health Economics		
	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: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

Two health technology assessment (HTA) bodies have published recommendations regarding canagliflozin in this indication: the Scottish Medicines Consortium and the National Institute for Health and Care Excellence. A summary of these recommendations is provided in Table 12.

TABLE 12: OTHER HTA FINDINGS

	NICE (2014)[29]	SMC (2014)[30]
Treatment	Canagliflozin 100 mg and 300 mg	
Price	Not reported	
Similarities with CDR submission	• Used a micro-simulation model with a 40-year time horizon • Modelled as triple therapy (metformin plus a sulfonylurea, and metformin plus TZD) • Use of NMA to elicit relative treatment effects • Inclusion of a metabolic drift assumption within the analysis where, over time and regardless of treatment, bio-markers such as A1C drift up	
Differences with CDR submission	• Modelled for dual therapy in combination with metformin, and compared with TZD (pioglitazone), a sulfonylurea, DPP-4 (sitagliptin), dapagliflozin and GLP-1 agonists (exenatide) • In triple therapy, canagliflozin was compared with GLP-1 agonists (exenatide) and long-acting insulin • Modelled as add-on to insulin therapy and compared with DPP-4 (sitagliptin) and GLP-1 agonists (exenatide)	

Manufacturer's results	**Dual therapy**
	• Canagliflozin (100 mg/300 mg) dominated by TZDs
	• Canagliflozin 100 mg, ICUR ($/QALY) vs.:
	  • Sulfonylurea: £1,537 (C$2,757)
	  • DPP-4: £97 (C$174)
	  • Dapagliflozin: £2,993 (C$5,368)
	  • GLP-1: £2,424[a] (C$4,348)
	• Canagliflozin 300 mg, ICUR ($/QALY) vs.:
	  • Sulfonylurea: £4,899 (C$8,787)
	  • DPP-4: £18,349 (C$32,911)
	  • Dapagliflozin: £21,626 (C$38,788)
	  • GLP-1: £76,214[a] (C$136,697)
	
	Triple therapy (without TZD)
	• Canagliflozin 100 mg, ICUR ($/QALY) vs.:
	  • DPP-4 dominated by canagliflozin
	  • GLP-1: dominated by canagliflozin
	  • Insulin: £263 (C$472)
	• Canagliflozin 300 mg, ICUR ($/QALY) vs.:
	  • DPP-4: £13,287 (C$23,832)
	  • GLP-1: Dominated by canagliflozin
	  • Insulin: £607 (C$1,089)
	
	Triple therapy (with TZD)
	• Canagliflozin 100 mg, ICUR ($/QALY) vs.:
		Dual therapy
		• Canagliflozin (100 mg/300 mg) dominated by TZDs
		• Canagliflozin 100 mg, ICUR ($/QALY) vs.:
		  • Sulfonylurea: £2,353 (C$4,220)
		  • DPP-4: £9,676 (C$17,355)
		  • Dapagliflozin: £8,220 (C$14,743)
		  • GLP-1: £77,706[a] (C$139,373)
		• Canagliflozin 300 mg, ICUR ($/QALY) vs.:
		  • Sulfonylurea: £5,600 (C$10,044)
		  • DPP-4: £26,875 (C$48,203)
		  • Dapagliflozin: £19,624 (C$35,198)
		  • GLP-1: £229,381[a] (C$411,418)
		
		Triple therapy (without TZD)
		• Canagliflozin 100 mg, ICUR ($/QALY) vs.:
		  • DPP-4: £2,158 (C$3,871)
		  • GLP-1: Dominant

	NICE (2014)[29]	SMC (2014)[30]

	• DPP-4: £1,095 (C$1,964)
	• GLP-1: Not reported
	• Insulin: Not reported
	
	• Canagliflozin 300 mg, ICUR ($/QALY) vs.:
	  • DPP-4: £21,430 (C$38,437)
	  • GLP-1: Not reported
	  • Insulin: Not reported
	Add-on to insulin
	• Canagliflozin 100 mg, ICUR ($/QALY) vs.:
	  • Dapagliflozin: dominated by canagliflozin
	  • DPP-4: £1,340[b] (C$2,339)
	  • GLP-1: £12,915[a] (C$23,164)
	• Canagliflozin 300 mg, ICUR ($/QALY) vs.:
	  • Dapagliflozin: £5,992 (C$10,747)
	  • DPP-4: £7,975 (C$14,304)
	  • GLP-1: £35,575[a] (C$63,807)
		• Insulin: £1,951 (C$3,499)
		• Canagliflozin 300 mg, ICUR ($/QALY) vs.:
		  • DPP-4: £22,187 (C$39,795)
		  • GLP-1: Dominant
		  • Insulin: £2,555 (C$4,383)
		
		Add-on to insulin
		• Canagliflozin 100 mg, ICUR ($/QALY) vs.:
		  • DPP-4 dominated
		  • GLP-1: £8,879[a] (C$15,925)
		• Canagliflozin 300 mg, ICUR ($/QALY) vs.:
		  • DPP-4: £6,250 (C$11,210)
		  • GLP-1: £132,540[a] (C$237,724)

Issues noted by the review group	• Not all comparators in the NICE scope had been included. • Comparators used were not always the most widely prescribed. • The NICE reference case states that data from head-to-head trials should be presented in the reference-case analysis if possible, but the manufacturer had instead sometimes used results from the meta-analyses. • It was not clear if the preference data for utility values wholly represented the population of England because they were derived from a European study.	• Although the metabolic drift assumption was deemed appropriate, concern was raised that the manufacturer assumed the drift occurs over a longer term than is appropriate. However, since the drift assumption was the same for canagliflozin and the comparator treatments, the concern was lessened. • Concern surrounding the appropriateness of using short-term outcome measures to estimate long-term treatment effects.
Results of reanalyses by the review group (if any)	• NICE found minimal variation in the dual-therapy ICURs when it reran the manufacturer's base-case analyses.	None reported
Recommendation	Canagliflozin in a dual-therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if: • a sulfonylurea is contraindicated or not tolerated, or • the person is at significant risk of hypoglycemia or its consequences. Canagliflozin in a triple-therapy regimen is recommended as an option for treating type 2 diabetes in combination with: • metformin and a sulfonylurea, or • metformin and a thiazolidinedione.	Accepted for restricted use within NHS Scotland: • Dual therapy in combination with metformin • Triple therapy in combination with metformin plus standard of care • Add-on to insulin therapy in combination with insulin plus standard of care.

	NICE (2014)[29]	SMC (2014)[30]
	Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.	

A1C = glycated hemoglobin; C$ = Canadian dollars; CDR = CADTH Common Drug Review; DPP-4 = dipeptidyl peptidase-4 inhibitors; GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; QALY = quality-adjusted life-year; SMC = Scottish Medicines Consortium; TZD = thiazolidinediones; vs = versus.

[a] Canagliflozin is both cheaper and less effective than GLP-1; therefore, ICUR is for GLP-1 to replace canagliflozin.

[b] Canagliflozin is both cheaper and less effective than DPP-4; therefore, ICUR is for DPP-4 to replace canagliflozin.

Note: £1.00 ≈ C$1.7936 (Bank of Canada, October 14, 2014).

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis comparing canagliflozin 100 mg and 300 mg to sitagliptin 100 mg as a third-line drug added to a combination of metformin plus a sulfonylurea, or metformin plus pioglitazone. The effectiveness of canagliflozin 300 mg was compared with sitagliptin 100 mg using data from the active-comparator randomized controlled trial (DIA3015).[2,4] For the canagliflozin 100 mg and sitagliptin 100 mg comparison, a network meta-analysis (NMA) was used to populate the analyses in the absence of head-to-head trial data. The reference-case time horizon was the patient's lifetime (up to 40 years) using the Canadian public payer perspective. The economic analyses were carried out using the Economics and Health Outcomes Model for type 2 diabetes mellitus (ECHO-T2DM).

The ECHO-T2DM is a second-order (parameter uncertainty) stochastic, patient-level micro-simulation model used to forecast long-term complications and cost consequences of anti-hyperglycemic drugs. The ECHO-T2DM model allows the use of the recent United Kingdom Prospective Diabetes Study (UKPDS) macrovascular and mortality risk equations from the UKPDS Outcomes Model 2 (UKPDS-OM2).[10] The equations were based on new data with a longer follow-up time of approximately 30 years (doubling to 89,760 patient-years).

The ECHO-T2DM generates cohorts of hypothetical patients defined by a set of characteristics, including demographics (e.g., age and gender), bio-marker values (e.g., glycated hemoglobin [A1C], systolic blood pressure [SBP], body mass index [BMI]), and disease indicators (e.g., disease duration and history of microvascular and macrovascular complications). The characteristics of these cohorts are sourced primarily from the baseline characteristics observed in randomized controlled trials.

In addition, the ECHO-T2DM simulates the progression of intermediary outcomes associated with microvascular complications such as microalbuminuria, foot ulceration, and diabetic neuropathy in addition to the end-stage culminations, such as end-stage renal disease, blindness, and amputation. The ECHO-T2DM allows the capture of differences in the costs and disutility at the relatively more common sub–end-stage level. The ECHO-T2DM also features a full chronic kidney disease (CKD) module based on the Centers for Disease Control and Prevention Model of CKD16, featuring actual kidney functioning as well as kidney disease.[11]

The ECHO-T2DM simulates the estimated glomerular filtration rate over time in interaction with kidney damage (microalbuminuria, macroalbuminuria, and end-stage renal disease), and it includes a number of adverse events that may be associated with the sodium-glucose cotransporter 2 mechanism of action like volume depletion, pollakiuria/polyuria/nocturia, upper and lower urinary tract infections, and genital mycotic infections.

Treatment effects from randomized controlled trials are used to modify patient bio-markers, which in turn modify the risks of complications over time. A treatment algorithm based on treatment threshold simulates treatment with antihyperglycemic drugs and concomitant treatment (anti-hypertensive, dyslipidemia) over time. When medication fails to control A1C, SBP, or low-density lipoprotein cholesterol adequately, treatment doses can be increased or new medications added. In addition to modifying patient bio-markers, treatment can result in increased risk for adverse events (e.g., severe

and non-severe hypoglycemic events, urinary tract infections, female and male genital mycotic infections, orthostatic volume depletion, osmotic-diuresis).

Microvascular, macrovascular, and mortality risk equations (including the new UKPDS-OM2 risk equations) convert each patient's characteristics into event risks. Monte Carlo techniques are then used to simulate which patients experience events and progress each year until the end of a user-defined time horizon ("death"). Subsequently, quality of life and economic consequences (costs) for competing treatment therapies are calculated.

The disutility weights associated with complications of type 2 diabetes mellitus were primarily sourced from the CADTH report.[6] Where suitable estimates were lacking, such as was the case for utility decrements associated with modelled treatment-related adverse events and excess weight, data were supplemented from the literature.[12-14] The manufacturer conducted a time–trade-off study to estimate utility values for selected health states, including gender-specific GMIs.[15] The disutility associated with excess weight was obtained from Bagust and Beale 2005.[16]

Unit costs for drugs were obtained from the Ontario Drug Benefit Formulary (2013)[17] when available. The price of sitagliptin was obtained from the Quebec public plan (2013).[18] For the base case, it was assumed that episodes of symptomatic non-severe hypoglycemia had no impact on the use of health service resources. Resource utilization associated with managing severe hypoglycemic episodes was derived from the same sources used for the CADTH Optimal Use Report on third-line pharmacotherapy for patients with type 2 diabetes mellitus.[6] Costs associated with managing long-term diabetes-related complications were obtained from several sources.[6,19-21]

TABLE 13: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	• Active-comparator, randomized controlled trial (DIA3015) was used to derive efficacy of canagliflozin 300 mg vs. sitagliptin 100 mg in patients on metformin plus a sulfonylurea[2-4] • Network meta-analysis was used to populate the analyses in the absence of head-to-head trial data[11]	Appropriate
Natural history	Natural history of T2DM was integrated in the model data from the United Kingdom Prospective Diabetes Study based on data with a follow-up time of approximately 30 years	Appropriate

Utilities	• Disutility weights associated with complications of T2DM primarily sourced from the CADTH Optimal Use Report[6]
	• Utility decrements associated with modelled treatment-related AEs and excess weight were supplemented from the literature:
	  • Disutility associated with weight gain was obtained from published literature (Bagust and Beale 2005)[16]
	  • Disutility weights associated with symptomatic non-severe and severe hypoglycemia events were sourced from a TTO study of over 1,600 individuals with T2DM (including patients from Canada)
		Likely appropriate

Adverse events (Indicate which specific adverse events were considered in the model)	AEs for blood glucose-lowering drugs that were considered in the model included: severe hypoglycemic events, symptomatic non-severe hypoglycemic events, upper and lower UTIs, and gender-specific GMIs	Appropriate

Data Input	Description of Data Source	Comment
Costs		
Drug	Unit costs for drugs were obtained from the Ontario public drug program (2013) when available; otherwise, prices were obtained from the Quebec public plan (2013)	
Event	Costs associated with managing long-term diabetes-related complications were obtained from several sources: • *CADTH Optimal Use Report: Third-Line Pharmacotherapy for Type 2 Diabetes – Update* (2013) • Ontario Ministry of Health • Expert opinion	

AE = adverse event; GMI = genital mycotic infection; T2DM = type 2 diabetes mellitus; TTO = time trade-off; UTI = urinary tract infection; vs = versus.

TABLE 14: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Treatment intensification was triggered when simulated A1C values were > 8%, a level approximating real-world treatment-switching patterns.	Likely appropriate
It was assumed that A1C for patients on canagliflozin, sitagliptin, and insulin would drift upwards at 0.15% per year. SBP and lipid values were also assumed to drift up over time, independent of treatment, at the following annual rates: 0.3 mm Hg for SBP; 0.00034 mmol/L (0.03 mg/dL) for triglycerides; and 0.00078 mmol/L (0.03 mg/dL) for other plasma lipids (i.e., TC, LDL cholesterol, and HDL cholesterol). BMI was assumed not to drift up over time.	Likely appropriate Clinical expert indicated that patients will experience upward drifts in A1C that will ultimately lead to insulin use
To be conservative, both disutility values for symptomatic non-severe hypoglycemia and severe hypoglycemia (–0.000004767 and –0.01, respectively) were used in the reference-case scenarios, as they were used in the *CADTH Optimal Use Report: Third-Line Pharmacotherapy for Type 2 Diabetes – Update* (2013)[6]	Appropriate
Patients in the canagliflozin groups were discontinued when the simulated eGFR fell below 45 mL/min/1.73 m^2 or if the patient developed ESRD.	Deemed appropriate by clinical expert
The utility reduction of 0.0061 per 1 kg/m^2 increase above a BMI of 25 was estimated by Bagust and Beale (2005);[16] it was derived using multivariate regression modelling and controlled for a large number of patient-specific factors whose omission would tend to confound estimates.	Likely appropriate The manufacturer had also conducted sensitivity analyses where the disutility with weight gain was changed to the CADTH report value (–0.001950) and excluded altogether.

A1C = glycated hemoglobin; BMI = body mass index; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure; TC = triglycerides.

Manufacturer's Results

In the first reference case (i.e., third-line therapy added to metformin plus a sulfonylurea), the manufacturer reported that canagliflozin 100 mg and 300 mg resulted in mean increases in quality-adjusted life-years (QALY) of 0.04 and 0.08, respectively, and were associated with lower costs ($981 and $2,035, respectively) over 40 years compared with sitagliptin 100 mg. In third-line therapy with

metformin plus pioglitazone, treatment with canagliflozin 300 mg and 100 mg resulted, respectively, in a mean increase of 0.08 QALY and 0.05 QALY. Treatment with canagliflozin 300 mg and 100 mg was also associated with lower costs of $683 and $492 over 40 years, compared with sitagliptin 100 mg.

TABLE 15: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASES

Base-Case Scenario	Incremental Cost ($)	Incremental QALY	Incremental LY	ICUR of Canagliflozin Versus Sitagliptin
Third-line therapy: metformin plus a sulfonylurea background				
1a) Canagliflozin 300 mg	–$2,035	+0.08	+0.05	Canagliflozin is dominant
1b) Canagliflozin 100 mg	–$981	+0.04	+0.02	
Third-line therapy: metformin plus pioglitazone background				
2a) Canagliflozin 300 mg	–$683	+0.08	+0.03	Canagliflozin is dominant
2b) Canagliflozin 100 mg	–$492	+0.05	+0.02	

ICUR = incremental cost-utility ratio; LY = life-year; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer's pharmacoeconomic submission, page 22, Table 8.11.[11]

In the metformin plus a sulfonylurea reference-case scenario, canagliflozin 300 mg and 100 mg were associated with increase in life-years of 0.05 and 0.02, respectively, compared with sitagliptin 100 mg. In the metformin plus pioglitazone reference scenario, the increase in life-years was 0.03 and 0.02 for canagliflozin 300 mg and 100 mg, respectively, compared with sitagliptin 100 mg.

Manufacturer's Sensitivity Analyses

Uncertainty was addressed using one-way deterministic sensitivity analyses that varied model parameters by using alternative values. The results indicate that canagliflozin 300 mg remained the least costly and most effective option in combination with metformin plus a sulfonylurea, or metformin plus pioglitazone. Canagliflozin 100 mg showed similar dominance in all sensitivity analyses of interest (discount rates, time horizons, A1C thresholds, and disutility weights around weight gain); it was only in the scenario of canagliflozin 100 mg with metformin plus pioglitazone that an incremental cost-utility ratio was observed (of $365 per QALY) when the time horizon was reduced to five years.

In addition, the manufacturer conducted scenario analyses addressing the use of canagliflozin as second-line therapy to correspond to the use of sitagliptin as second-line therapy in Ontario and Quebec, as well as scenario analyses when canagliflozin dosing is titrated. Results show canagliflozin 100 mg and 300 mg dominating sitagliptin 100 mg both as second-line therapy and when doses are increased in third-line therapy.

TABLE 16: SUMMARY OF RESULTS OF THE MANUFACTURER'S SCENARIO ANALYSES

	Incremental Costs	Incremental QALYs	ICUR
Dose increase in third-line therapy sensitivity analysis			
Canagliflozin 100 mg or 300 mg vs. sitagliptin 100 mg (metformin plus a sulfonylurea)[a]	–$1,062	0.06	Dominant
Canagliflozin 100 mg or 300 mg vs. sitagliptin 100 mg (metformin plus pioglitazone)[b]	–$925	0.06	Dominant
Second-line therapy sensitivity analysis (plus metformin)[c]			
Canagliflozin 300 mg vs. sitagliptin 100 mg	–$1,317	0.07	Dominant
Canagliflozin 100 mg vs. sitagliptin 100 mg	–$800	0.04	Dominant

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs = versus.
[a] Patient-level data from clinical trial DIA3012 and network meta-analysis for efficacy and adverse events.[22]
[b] Patient-level data from clinical trial DIA3002 and network meta-analysis for efficacy and adverse events.[23]
[c] Patient-level data on efficacy and adverse events from clinical trial DIA3006.[11]
Source: Adapted from manufacturer's pharmacoeconomic submission, page 34, Tables 8.14 and 8.15.[11]

Probabilistic Sensitivity Analysis

The cost-effectiveness acceptability curves indicate that canagliflozin 100 mg and 300 mg have high likelihoods of being cost-effective versus sitagliptin 100 mg at all levels of willingness-to-pay for an additional QALY for both base cases (metformin plus a sulfonylurea and metformin plus pioglitazone). For base case 1, with no willingness-to-pay for a QALY (i.e., at the origin of $0), canagliflozin 300 mg and 100 mg are nearly 100% and 60% likely to be cost-effective, respectively. For base case 2, with no willingness-to-pay for a QALY (i.e., at the origin of $0), canagliflozin 300 mg and 100 mg are almost 75% and 70% likely to be cost-effective, respectively.

CADTH Common Drug Review Reanalysis

The manufacturer's base-case comparison was for canagliflozin (300 and 100 mg) as a third-line drug added on to metformin plus a sulfonylurea, or metformin plus pioglitazone background. However, based on discussion with the clinical expert on this review, it was determined that patients with a metformin plus pioglitazone background constitute a minority among type 2 diabetes patients in Canada due to the risk of congestive heart failure in patients using thiazolidinediones.[6] Therefore, CDR reanalyses will be focused on canagliflozin being added on to metformin plus a sulfonylurea background.

Based on the variability of sources used by the manufacturer in obtaining the effect estimates for canagliflozin 100 mg and the potential for direct trial estimates to contradict the results from the NMA, the CDR conducted one-way sensitivity analyses on several parameters (A1C, SBP, BMI, hypoglycemic events, treatment discontinuation rate, and disutility with weight gain) to assess the robustness of the manufacturer's results. Given the variability in reimbursement costs paid by public drug plans in Canada for dipeptidyl peptidase-4 inhibitors, the one-way sensitivity analyses were also conducted using the lowest price of a DPP-4 inhibitor covered by a public drug ($2.25 per 5 mg tablet of linagliptin):[7]

- **Assume similar treatment effects on A1C and using sitagliptin A1C treatment effects for both treatment groups:** The NMA did not show statistically significant differences between canagliflozin 100 mg and sitagliptin 100 mg in terms of effects on A1C; however, the estimates used by the manufacturer numerically favoured sitagliptin 100 mg over canagliflozin 100 mg. A CDR reanalysis used the sitagliptin 100 mg effect on A1C for both canagliflozin 100 mg and sitagliptin 100 mg.

- **Assume similar rate of severe hypoglycemic events:** Although the NMA did not show statistically significant differences between canagliflozin 100 mg and sitagliptin 100 mg in terms of hypoglycemic events, the estimates used by the manufacturer numerically favoured canagliflozin 100 mg (0.014 events per patient-year) over sitagliptin 100 mg (0.019 events per patient-year). A CDR reanalysis used a rate of 0.014 for both canagliflozin 100 mg and sitagliptin 100 mg.
- **Assume different treatment effects for sitagliptin 100 mg on BMI:** A CDR reanalysis used the lower bound of the credible interval for the treatment effect of sitagliptin 100 mg versus canagliflozin 100 mg.
- **Assume higher rate of discontinuation of sitagliptin due to adverse events based on one-year data from trial DIA3015:** In the manufacturer's base-case analysis comparing canagliflozin 100 mg to sitagliptin 100 mg, the discontinuation rate for sitagliptin due to adverse events was derived from 26-week data from trial DIA3015.[11] However, the model's cycle length was one year, and the DIA3015 trial had reported one-year discontinuation rates for sitagliptin 100 mg due to adverse events; therefore, a CDR reanalysis was conducted using the one-year data instead of the 26-week data in the base-case analysis.
- **Assume lower treatment effect on SBP for sitagliptin using lower bound of credible interval from NMA:** In the base case, the manufacturer used the mean value from the NMA to represent the treatment effect of sitagliptin on SBP. Heterogeneity limitations about the NMA raise uncertainty over the resulting treatment effects. CDR conducted a reanalysis using a more conservative estimate for sitagliptin.
- **Disutility associated with weight gain using lower price of sitagliptin 100 mg:** The manufacturer's submission included a one-way sensitivity analysis using a disutility value for weight gain derived from the 2013 CADTH Optimal Use Report (–0.001950)[6] instead of the disutility value of –0.0061 derived from Bagust et al. (2005);[16] however, the analysis was done using only the manufacturer-submitted price of $2.6177. CDR conducted a one-way sensitivity analysis using the disutility value from the CADTH Optimal Use Report and a lower price for sitagliptin 100 mg of $2.25.

Results of CDR one-way sensitivity analyses on A1C, SBP, BMI, severe hypoglycemic events, and discontinuation rates at the manufacturer-submitted price for canagliflozin ($2.62 per day) show canagliflozin 300 mg and 100 mg continuing to dominate sitagliptin 100 mg (i.e., producing more QALYs at less cost), thus indicating the robustness of the manufacturer's results.

TABLE 17: COMPLETE RESULTS FROM CDR REANALYSES

	Canagliflozin 100 mg			Sitagliptin 100 mg			Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
	Total Cost ($)	Drug Costs	Total QALY	Total Cost ($)	Drug Cost	Total QALY			
Base-case price of $2.6177 for sitagliptin 100 mg									
Similar effect on A1C	44,176	9,958	8.37	45,567	10,846	8.31	–1,391	0.05	Dominating
Sitagliptin effect on SBP (0.28)	44,921	9,946	8.35	45,697	10,840	8.31	–776	0.04	Dominating
Sitagliptin effect on BMI (–0.01)	44,621	9,962	8.35	45,554	10,855	8.32	–933	0.03	Dominating
Event rate for moderate hypoglycemia for sitagliptin (1.37)	44,402	9,909	8.32	45,407	10,791	8.27	–1,005	0.04	Dominating
Event rate for severe hypoglycemia for sitagliptin (0.014)	44,684	9,949	8.35	45,575	10,838	8.30	–891	0.04	Dominating
Discontinuation rate due to adverse events for sitagliptin (0.037)	44,466	9,938	8.36	45,433	10,634	8.30	–967	0.06	Dominating
Disutility from weight gain (0.001950)	44,637	9,957	8.74	45,494	10,846	8.72	–857	0.02	Dominating
Lower price of $2.25 for sitagliptin 100 mg									
No changes to effects	44,637	9,957	8.36	43,964	9,316	8.32	673	0.04	15,558
Similar effect on A1C	44,176	9,958	8.37	44,037	9,316	8.31	139	0.05	2,563
Sitagliptin effect on SBP (0.28)	44,921	9,946	8.35	44,168	9,311	8.31	753	0.04	18,057
Sitagliptin effect on BMI (–0.01)	44,621	9,962	8.35	44,023	9,324	8.32	598	0.03	22,440
Event rate for moderate hypoglycemia for sitagliptin (1.37)	44,402	9,909	8.32	43,885	9,269	8.27	518	0.04	11,704
Event rate for severe hypoglycemia for sitagliptin (0.014)	44,796	9,945	8.33	43,939	9,308	8.29	857	0.04	23,280

	Canagliflozin 100 mg			Sitagliptin 100 mg			Incremental Cost ($)	Incremental QALY	ICUR ($/QALY)
	Total Cost ($)	Drug Costs	Total QALY	Total Cost ($)	Drug Cost	Total QALY			
Discontinuation rate due to adverse events for sitagliptin (0.037)	44,693	9,929	8.33	43,979	9,136	8.29	715	0.04	16,421
Disutility from weight gain (0.001950)	44,637	9,957	8.74	43,964	9,316	8.72	673	0.02	35,150
Canagliflozin 300 mg using lower price for sitagliptin 100 mg at $2.25	44,136	9,859	8.42	44,672	9,130	8.34	–536	0.08	Dominating

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

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