Common Drug Review
Pharmacoeconomic Review Report

April 2016

Drug	Dapagliflozin (Forxiga)
Indication	For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.
Listing request	For the treatment of patients with type 2 diabetes mellitus to improve glycemic control when added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.
Dosage form(s)	5 mg and 10 mg oral tablets
NOC date	December 2, 2015
Manufacturer	AstraZeneca Canada Inc.

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

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ABBREVIATIONS

A1C	glycated hemoglobin
AE	adverse event
BMI	body mass index
CDR	CADTH Common Drug Review
DPP-4	dipeptidyl-peptidase 4
ESRD	end-stage renal disease
GI	genital infection
GLP-1	glucagon-like peptide-1
ICUR	incremental cost-utility ratio
NMA	network meta-analysis
QALY	quality-adjusted life-year
SBP	systolic blood pressure
SE	standard error
SGLT-2	sodium-glucose cotransporter 2
T2DM	type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Dapagliflozin 5 mg and 10 mg tablets
Study Question	To assess the cost-effectiveness of dapagliflozin when initiated as add-on therapy to MET + SU in a Canadian population of T2DM patients. The base-case analysis was conducted in context of the requested listing, for patients for whom insulin is not an option.
Type of Economic Evaluation	CUA
Target Population	Patients with T2DM who have inadequate glycemic control on MET + SU, for whom insulin is not an option
Treatment	Dapagliflozin 5 mg or 10 mg daily as add-on to MET + SU
Outcome	QALYs
Comparators	MET + SU + DPP-4 inhibitor
Perspective	Canadian public payer
Time Horizon	Lifetime (up to 40 years)
Results for Base Case	Dapagliflozin (5 mg or 10 mg) vs. DPP-4 inhibitor as add-on to MET + SU: dapagliflozin is dominant — associated with greater health gains and lower total costs
Key Limitations	CDR noted the following limitations with the manufacturer's submission: • The results were sensitive to weight-related utility values. Smaller disutility values associated with weight gain have been reported in the literature, and there is uncertainty surrounding the manufacturer's assumption of utility gain associated with weight loss. The use of more conservative assumptions and estimates reduces the cost-effectiveness value of dapagliflozin and may change the conclusion of the manufacturer's base-case analysis. • The base-case analysis has not conservatively considered the variability in the pricing of DPP-4 inhibitors across CDR-participating drug plans. The costing of lower-priced options would impact the cost-effectiveness results by favouring dapagliflozin less. • The manufacturer did not clearly assess the cost-effectiveness of dapagliflozin in context of the dosage options (5 mg or 10 mg), having not included the 5 mg data in the NMA used to populate the model. There is a lack of clarity in the cost-effectiveness of the use of the daily 5 mg dosage. • Comparative efficacy for dapagliflozin was based on a manufacturer-funded NMA. Heterogeneity was noted. • The manufacturer assumed full compliance to treatment and no treatment discontinuation over time in the base-case analysis for compared interventions; however, it is very likely that more patients in the dapagliflozin group will discontinue treatment due to renal impairment over the model lifetime horizon, which would reduce the demonstrated cost-effectiveness benefit of dapagliflozin. • There is uncertainty around the long-term efficacy of compared treatments, and around the generalization of the model structure to the Canadian context, as the model was informed by natural history data from the UK.
CDR Estimates	• CDR performed a number of reanalyses. Results were most sensitive to utility values associated with change in weight. • When using alternate (smaller) disutility values associated with weight gain, assuming no change in utility from weight loss and reduced price for DPP-4

Drug Product	Dapagliflozin 5 mg and 10 mg tablets
	inhibitors, the ICUR ranged from $8,259 to $71,360 per QALY for dapagliflozin vs. DPP-4 inhibitors. • Using a shorter time horizon of 10 years, the ICUR for CDR reanalyses using smaller disutility values associated with weight gain and a reduced price for DPP-4 inhibitors ranged from $7,571 to $108,246 per QALY for dapagliflozin vs. DPP-4 inhibitors. • For the above presented reanalyses, when assuming the same price for dapagliflozin and DPP-4 inhibitors (same tablet/daily price), dapagliflozin dominates DPP-4 inhibitors, being more effective and less costly.

CDR = CADTH Common Drug Review; CUA = cost-utility analysis; DPP-4 = dipeptidyl-peptidase 4; ICUR = incremental cost-utility ratio; MET = metformin; NMA = network meta-analysis; QALY = quality-adjusted life-year; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; vs. = versus.

EXECUTIVE SUMMARY

Background

Dapagliflozin (Forxiga) is an oral antihyperglycemic drug of the sodium-glucose cotransporter 2 (SGLT2) inhibitor class. This CADTH Common Drug Review (CDR) focuses on dapagliflozin for the treatment of patients with type 2 diabetes mellitus (T2DM) to improve glycemic control when added on to metformin and a sulfonylurea for patients with inadequate glycemic control on combination therapy with metformin and a sulfonylurea and for whom insulin is not an option.

The recommended starting dose of dapagliflozin is 5 mg once daily and can be increased to 10 mg daily for additional glycemic control.[1] The manufacturer submitted a confidential flat price of [redacted] per 5 mg and 10 mg tablet.[2]

The manufacturer submitted a cost-utility analysis of dapagliflozin compared with a dipeptidyl-peptidase 4 (DPP-4) inhibitor as add-on therapy to metformin and a sulfonylurea in patients with T2DM for whom insulin is not an option, using the previously validated Cardiff Diabetes Model,[3,4] a UK model that can accommodate type 2 diabetic and nondiabetic populations using the United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine formula and the Framingham risk equation, respectively.[5] The time horizon was the patient's lifetime (up to 40 years) using a Canadian public payer perspective. Efficacy data for the comparison were obtained from a manufacturer-funded network meta-analysis (NMA).[6]

The manufacturer reported that dapagliflozin dominated DPP-4 inhibitors when used as add-on to metformin and a sulfonylurea. Sensitivity analyses conducted by the manufacturer indicated the base-case results were robust to changes in individual parameters.

Summary of identified limitations and key results

CDR identified several limitations with the submitted economic analysis. Key limitations were associated with the fact that the results from the cost-utility analysis were sensitive to the utility changes applied to weight gain/weight loss, and also to drug costs. There is variability in the reported utility values associated with weight gain and uncertainty around the validity of applying an increased utility for weight lost, as well as variability in the pricing of DPP-4 inhibitors across participating CDR drug plans. Another limitation is the inability to consider the cost-effectiveness of dapagliflozin 5 mg, as recommended dosing of dapagliflozin starts at 5 mg and can be increased to 10 mg if additional glycemic control is needed, and the NMA used to populate the model has not included the dapagliflozin 5 mg studies. Furthermore, although the manufacturer conducted a scenario analysis that included discontinuation due to renal impairment for dapagliflozin that is highly probable based on the progressive nature of diabetes, the discontinuation rate used by the manufacturer was considered low by the clinical expert. Finally, there is uncertainty around the long-term efficacy of treatments, and around the generalization to the Canadian context of the model structure, which was informed by natural history data from the UK.

CDR analyses used alternative (smaller) disutility values associated with weight gain, and assumed no utility gain associated with weight loss because of uncertainty with the evidence that weight loss alone would equate to improved quality of life, and because of the possibility of double-counting this effect with the model, which applies disutility to comorbidities that correlate with weight change. Furthermore, due to variability in DPP-4 inhibitor pricing and reimbursement across Canada, and a previous CADTH Canadian Drug Expert Committee (CDEC) recommendation for canagliflozin (i.e., drug

plan costs for canagliflozin should not exceed the drug plan cost of DPP-4 inhibitors),[7] CDR considered different relative prices for dapagliflozin and linagliptin (based on the lowest list price for a DPP-4 inhibitor of $2.25 daily, from the Nova Scotia public drug formulary, November 2015).[8] As well, CDR used the price of a DPP-4 inhibitor plus metformin combination product (based on the lowest list price of $2.54 daily, from the Ontario Drug Benefit, November 2015),[9] while the manufacturer base-case analysis used a daily price of $2.55 and $0.23 for DPP-4 inhibitor and metformin, respectively (based on Ontario Drug Benefit price). The CDR base case, assuming different disutility values for weight gain and no change of utility for weight loss, and using the Nova Scotia price of linagliptin as the DPP-4 inhibitor, resulted in an incremental cost-utility ratio (ICUR) for dapagliflozin compared with a DPP-4 inhibitor as add-on to metformin and a sulfonylurea that ranged from $8,259 to $71,360 per quality-adjusted life-year (QALY) (wide range driven by utility values associated with weight gain). When applying to this a time horizon of 10 years instead of 40 years, dapagliflozin dominated the DPP-4 inhibitor. Finally, when the same price was assumed for both dapagliflozin and DPP-4 inhibitor for all the above described scenarios, dapagliflozin dominated DPP-4 inhibitor.

Conclusions

The evidence presented by the manufacturer to support the cost-effectiveness of dapagliflozin as a third-line treatment added on to metformin and a sulfonylurea was based on a 10 mg daily dosing. The cost-effectiveness of dapagliflozin 5 mg daily versus other comparators remains unknown.

Results were mostly sensitive to utility values associated with weight changes, comparative pricing of dapagliflozin with DPP-4 inhibitors, and model time horizon.

CDR found that the ICUR for dapagliflozin versus a DPP-4 inhibitor could be as high as $71,360 per QALY when added to metformin and a sulfonylurea over 40 years. Incremental costs associated with dapagliflozin compared with DDP-4 inhibitors were based on drug costs and the increased risk of urogenital infections, while incremental QALYs were small and driven by benefits of dapagliflozin on weight gain, ranging from 0.01 to 0.02 QALYs over 40 years compared with DPP-4 inhibitors.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

Summary of the manufacturer's pharmacoeconomic submission

The manufacturer submitted a cost-utility analysis of dapagliflozin as add-on therapy to metformin and a sulfonylurea. The reference case time horizon was the patient's lifetime (up to 40 years) using the Canadian public payer perspective.[4]

Efficacy data for combination therapy of metformin and a sulfonylurea plus a dipeptidyl-peptidase 4 (DPP-4) inhibitor versus combination therapy of metformin and a sulfonylurea plus dapagliflozin were obtained from a manufacturer-funded network meta-analysis (NMA).[6] The outcomes from the NMA used to inform the economic model were change from baseline in glycated hemoglobin (A1C), weight, and systolic blood pressure (SBP), and the probabilities of symptomatic and severe hypoglycemia (based on the proportion of patients with at least one episode). In the NMA, drugs and doses from a specific class were pooled together regardless of frequency or mode of administration. Comparisons between dapagliflozin and DPP-4 inhibitors showed no statistically significant differences in A1C, SBP, and the odds ratios of hypoglycemic events. Dapagliflozin was associated with statistically significant reductions in weight compared with DPP-4 inhibitors.

The economic analyses were carried out using the Cardiff Diabetes Model.[3] The Cardiff Diabetes Model is a validated, fixed-time-increment stochastic simulation designed to evaluate the impact of new therapies in a cohort of up to 10,000 hypothetical patients over a period of 40 years. The cohorts of hypothetical patients are defined by a set of baseline characteristics including demographics (e.g., age and gender), biomarker values (e.g., A1C, SBP, and body mass index [BMI]), and disease indicators (e.g., disease duration and history of microvascular and macrovascular complications). The time-dependent evolution of risk factors and prediction of cardiovascular and microvascular complications are implemented using the equations reported in the United Kingdom Prospective Diabetes Study (UKPDS) macrovascular and mortality risk equations.[5] The model simulates the progression of intermediate outcomes associated with microvascular complications, such as microalbuminuria, foot ulceration, and diabetic neuropathy, in addition to end-stage culminations including end-stage renal disease (ESRD), blindness, and amputation. Standard outputs from model simulations include the incidence of microvascular (retinopathy, neuropathy, or nephropathy) and macrovascular complications (congestive heart disease, myocardial infarction [MI], sudden death, and cerebrovascular disease defined as neurological deficit with symptoms or signs lasting one month or more), mortality, cost-effectiveness and cost-utility data, and acceptability curves.[5]

The majority of disutility weights associated with complications of T2DM were obtained from the UKPDS 62,[10] with the exception of ESRD, which was sourced from a published study by Currie et al.[11] The health utility of changes in BMI used in the analysis was based on a manufacturer-funded Canadian study that estimated utilities using a time trade-off utility valuation method for a set of six weight-related type 2 diabetes mellitus (T2DM) health states from 96 Canadian T2DM patients with a mean age of 55 years and a mean BMI of 32 kg/m^2.[12] The study reported by Lane et al.[12] showed that for every one unit increase in BMI, there was an associated decrease in utility of 0.0472, and for every unit decrease in BMI, there was an associated increase in utility of 0.0171.[12] Disutility weights associated with hypoglycemia were sourced from the CADTH Optimal Use report for third-line pharmacotherapy in T2DM.[9] Utility decrements related to the occurrence urinary tract infection (UTI) and genital infection were derived from a published economic evaluation of care interventions for UTIs in women.[13]

The manufacturer assumed that episodes of mild/moderate hypoglycemia had no impact on health care resource use.[4] Costs associated with managing severe hypoglycemic episodes were derived from published reports.[14] Costs associated with managing long-term diabetes-related complications and treating adverse events (AEs) were obtained from published sources.[9,15,16] The manufacturer applied the cost of the least expensive DPP-4 inhibitor (linagliptin) using the Ontario Drug Benefit price.[17]

Manufacturer's base case

The results of the manufacturer's base-case analysis showed that dapagliflozin dominated when compared with DPP-4 inhibitors when added on to metformin and a sulfonylurea (less costly, more effective). Table 2 presents the detailed results of the manufacturer base case.

TABLE 2: MANUFACTURER BASE-CASE RESULTS

	MET + SU + dapagliflozin		MET + SU + DPP-4 Inhibitor		Difference	
Events	Non-fatal	Fatal	Non-fatal	Fatal	Non-fatal	Fatal
Macrovascular						
Ischemic heart disease	124.35	0.00	124.64	0.00	–0.29	0.00
Myocardial infarction	118.18	182.88	118.68	183.27	–0.50	–0.39
Congestive heart failure	78.70	26.77	79.29	26.92	–0.59	–0.15
Stroke	94.59	11.85	94.97	11.85	–0.38	0.00
Microvascular						
Blindness	70.37	0.00	70.46	0.00	–0.08	0.00
Nephropathy	40.04	5.15	40.40	5.16	–0.36	0.00
Amputation	62.88	8.19	63.25	8.18	–0.37	0.00
Adverse events						
Urinary tract infection	1,651.07		745.60		905.47	
Genital infection	1,447.22		0.00		1,447.22	
Hypoglycemia (symptomatic)	6,172.20		5,055.62		1,116.58	
Hypoglycemia (severe)	14.96		12.12		2.84	
Costs						
Drug treatment (total)	$13,366.64		$13,832.89		–$466.25	
Severe hypoglycemia	$1.21		$0.98		$0.23	
Other AE (UTI, genital infection)	$137.98		$33.22		$104.76	
IHD	$2,573.08		$2,589.74		–$16.65	
MI	$3,953.24		$3,979.98		–$26.74	
Stroke	$2,524.24		$2,566.33		–$42.09	
CHF	$2,841.39		$2,858.70		–$17.31	
Blindness	$905.44		$906.08		–$0.63	
Nephropathy	$1,742.01		$1,778.22		–$36.21	
Amputation	$2,563.23		$2,592.17		–$28.94	
Total costs	**$30,608.47**		**$31,138.30**		**–$529.83**	

	MET + SU + dapagliflozin	MET + SU + DPP-4 Inhibitor	Difference
QALYs	**10.692**	**10.583**	**0.109**
ICUR			**Dominant[a]**

AE = adverse event; CHF = congestive heart failure; DPP-4 = dipeptidyl-peptidase 4; ICUR = incremental cost-utility ratio; IHD = ischemic heart disease; MET = metformin; MI = myocardial infarction; QALY = quality-adjusted life-year; SU = sulfonylurea; UTI = urinary tract infection.
[a] A dominant option is associated with greater health gains and lower total costs.
Source: Adapted from manufacturer's pharmacoeconomic submission, Tables 7.2 and 7.3 (page 48).[4]

Summary of manufacturer's sensitivity analyses

Uncertainty was addressed using one-way deterministic sensitivity analyses that varied model parameters by using alternative values, and scenario analyses to determine impact of alternative assumptions and data sources on model results (discount rates, time horizon, background clinical history, UKPDS equations, blood pressure, test strips reimbursement, cost and disutility of mild/moderate hypoglycemia, disutility of severe hypoglycemia, choice and cost of comparator, discontinuation due to renal impairment, inclusion of diabetic ketoacidosis as an AE, and NMA structure). The results of the majority of sensitivity analyses indicated that dapagliflozin remained the least costly and most effective option when added to metformin and a sulfonylurea. Sensitivity analyses performed by the manufacturer indicated the base-case conclusion was sensitive to change in the cost for the comparator (DPP-4 inhibitor; changed from $2.55 [5 mg tablet of linagliptin, Ontario Drug Benefit price] to the lowest publicly available price: $2.25 per 5 mg tablet of linagliptin, Nova Scotia Drug Plan, accessed November 2015)[8]. The resulting incremental cost-utility ratio (ICUR) in this scenario was $8,259 per quality-adjusted life-year (QALY).

The manufacturer conducted a probabilistic sensitivity analysis by simulating 1,000 cohorts of 1,000 patients, in which values of key parameters were drawn randomly and independently from the parameter distributions. Standard errors (SEs) were used for the parameter distribution if available, otherwise the manufacturer assumed the SE to be 20% of the mean, except for costs where SE was assumed to be 10%.[4] Beta distributions were used for utilities and probability estimates, gamma distributions were used for costs, and normal distributions were used for the other parameters.[4] The cost-effectiveness acceptability curves indicate that dapagliflozin had a 55% likelihood of being cost-effective versus DPP-4 inhibitor when added to metformin and a sulfonylurea at a threshold of $10,000 per QALY.

Limitations of manufacturer's submission

- **Uncertainty with weight-related utility values:** The manufacturer's model applied a utility reduction of 0.0472 per 1 unit increase in BMI, and a utility increase of 0.0171 for every unit decrease in BMI throughout the duration of the analysis, based on Lane et al., a manufacturer-funded Canadian utility elicitation study that derived the utility estimates from 96 T2DM patients (N = 96).[12] As there is no evidence to associate long-term weight loss with improvements in clinical outcomes or quality of life,[18-20] and changes in weight being considered a subjective experience with different ways of impacting individuals, the reliability, uncertainty, and generalizability of the manufacturer-funded study results warrants cautious consideration. Additionally, potential double-counting of this change in quality of life may occur as the model structure applies disutility to comorbidities that correlate with weight change. Further, other studies, such as Bagust et al. (N = 4,641), and a previous CADTH Therapeutic Review on therapies for T2DM reported smaller disutility values associated with weight gain (0.0061 and 0.00195, respectively).[9,15,21] Therefore, reanalyses

were conducted by CADTH Common Drug Review (CDR) reviewers that excluded utility increments from weight loss and used only alternate disutility values for weight gain, as reported in the literature.[9,15,21]

- **Variability in the pricing of DPP-4 inhibitor:** The manufacturer selected the price for linagliptin 5 mg for the DPP-4 inhibitor comparator to dapagliflozin as add-on treatments to metformin and a sulfonylurea. The price for linagliptin in the model for the base-case analysis was based on the Ontario Drug Benefit price ($2.55 per 5 mg tablet).[17] Consistent with the CADTH review on therapies for T2DM and as tested by the manufacturer in its sensitivity analysis, CDR reviewers considered the lowest price of a DPP-4 inhibitor publicly available in Canada (linagliptin 5 mg; $2.25, Nova Scotia Drug Plan, November 2015).[8]
- **The model does not allow assessment of the cost-effectiveness of the dapagliflozin 5 mg dose:** The manufacturer's efficacy estimate for dapagliflozin in the economic model was based on the submitted NMA that included only data for dapagliflozin 10 mg.[6] The manufacturer has requested the listing of both doses of dapagliflozin (5 mg and 10 mg daily) as add-on treatments to metformin and a sulfonylurea in patients with T2DM. The manufacturer's economic evaluation is based on clinical efficacy data of dapagliflozin only at 10 mg daily;[6] no evidence was submitted to support the assumption that the efficacy of dapagliflozin at 5 mg (when used in appropriate context) on A1C, weight loss, and SBP would be similar to that of dapagliflozin at 10 mg daily. Therefore, the cost-effectiveness of dapagliflozin in a population receiving dapagliflozin 5 mg is unclear.
- **Limitations with the submitted NMA:** The NMA submitted by the manufacturer pooled data across drug classes regardless of dosage strength, frequency, or mode of administration, and did not include data on the clinical efficacy of dapagliflozin at a dose of 5 mg daily. Other limitations noted in the CDR clinical report included heterogeneity across some studies and results of the NMA not analyzed by time point, and exclusion of other third-line treatments for T2DM.
- **Assumption of 100% compliance with no treatment discontinuation:** The product monograph for dapagliflozin indicates that it is contraindicated in patients with moderate to severe renal impairment (defined as an estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73m^2 or ESRD).[1] In such patients, dapagliflozin did not improve glycemic control, and adverse reactions were more frequent.[1] However, the manufacturer's base-case analysis did not account for any treatment discontinuation related to moderate to severe renal impairment. It is expected that more discontinuations with dapagliflozin will occur compared with DPP-4 inhibitor due to moderate to severe renal impairment; this is more than the proportion proposed by the manufacturer in its sensitivity analysis.
- **Uncertainty concerning the long-term cost-effectiveness of the compared interventions:** There is uncertainty about the long-term efficacy of compared treatments, which limits the validity of the model's long-term results. Additionally, the generalization to the Canadian context of the model used by the manufacturer may be questioned, as the predictive structure was informed by UK natural history data.

Utilities associated with changes in body mass index

Based on the uncertainty associated with deriving the utility/disutility estimates associated with weight changes by the manufacturer, CDR reanalyses were conducted assuming no utility increment with weight loss, and using disutility associated with weight gain from alternate published sources: Bagust et al. (–0.0061) and a previous CADTH Therapeutic Review (–0.00195).[9,15,21]

Variability in the pricing of DPP-4 inhibitors

Given the variability in reimbursement costs for DPP-4 inhibitors across public drug plans in Canada, one-way sensitivity analyses were also conducted using the lowest price of a DPP-4 inhibitor covered by

a CDR-participating drug plan ($2.25 per 5 mg tablet of linagliptin, Nova Scotia Drug Plan, accessed November 2015).[8] Additional analyses were conducted using the same lowest price of a DPP-4 inhibitor for both comparators (i.e., dapagliflozin and DPP-4 inhibitor), as well as using the lowest price of a DPP-4 inhibitor plus metformin combination product ($1.27 per 2.5 mg saxagliptin/1,000 mg metformin tablet, $2.54 per day, Ontario Drug Benefit, accessed November 2015).[17] The manufacturer's base-case analysis used a daily price of $2.55 and $0.23 per day, for a DPP-4 inhibitor and metformin, respectively (Ontario Drug Benefit price).

Multi-way analyses

CDR also conducted multi-way sensitivity analyses considering the CDR assumptions described above for utility and disutility associated with weight changes, and using the lower publicly available price of $2.25 for linagliptin.[8] The summary results are presented in Table 3. Based on uncertainty with extrapolation of treatment effects beyond trial duration over an extended time horizon and uncertainty with treatment discontinuation and patient compliance rates, additional one-way reanalyses were conducted by CDR using a shorter time horizon of 10 years (Table 4) (refer to Appendix 5: Reviewer Worksheets for further details.

TABLE 3: RESULTS OF CADTH COMMON DRUG REVIEW REANALYSES FOR DAPAGLIFLOZIN VERSUS DPP-4 INHIBITOR AS ADD-ON TO METFORMIN AND A SULFONYLUREA

		Inputs	Source	Incremental Cost	Incremental QALY	ICUR
Base Case[a]	Increase BMI Decrease BMI	–0.0472 0.0171	Lane et al.[12]	**–$530**	**0.109**	**Dominant**[b]
Base-case[a] analysis using reduced DPP-4 inhibitor price ($2.25)				**$901**	**0.109**	**$8,259**
Base-case[a] analysis using the price of a DPP-4 inhibitor/metformin combination ($2.54 per day)				**$638**	**0.109**	**$5,846**
Alternative utility inputs						
Disutility with weight gain[c]		0.00195	CADTH[9,15]	–$530	0.013	Dominant[b]
		0.0061	Bagust et al.[21]		0.020	Dominant[b]
Alternative utility inputs using reduced DPP-4 inhibitor price ($2.25 per tablet)						
Disutility with weight gain[c]		0.00195	CADTH[9,15]	$901	0.013	$71,360
		0.0061	Bagust et al.[21]		0.020	$44,635
Alternative utility inputs using reduced dapagliflozin and DPP-4 inhibitor price ($2.25)						
Disutility with weight gain[c]		0.00195	CADTH[9,15]	–$54	0.013	Dominant[b]
		0.0061	Bagust et al.[21]		0.020	Dominant[b]
Alternative utility inputs using price of DPP-4 inhibitor + MET combination product ($2.54 per day)						
Disutility with weight gain[c]		0.00195	CADTH[9,15]	$638	0.013	$50,512
		0.0061	Bagust et al.[21]		0.020	$31,594

BMI = body mass index; DPP-4 = dipeptidyl-peptidase 4; ICUR = incremental cost-utility ratio; MET = metformin; QALY = quality-adjusted life-year.

[a] Manufacturer base case.

[b] A dominant option is associated with greater health gains and lower total costs.

[c] No utility gain with weight loss was applied.

TABLE 4: RESULTS OF CADTH COMMON DRUG REVIEW REANALYSES FOR DAPAGLIFLOZIN VERSUS DPP-4 INHIBITOR AS ADD-ON TO METFORMIN AND A SULFONYLUREA USING 10-YEAR TIME HORIZON

		Inputs	Source	Incremental Cost	Incremental QALY	ICUR
Base Case[a]	Increase BMI Decrease BMI	–0.0472 0.0171	Lane et al.[12]	**–$530**	**0.109**	**Dominant**[b]
Base-case[a] analysis using 10-year time horizon				**–$332**	**0.067**	**Dominant**[b]
Base-case[a] analysis using 10-year time horizon and reduced DPP-4 inhibitor price ($2.25)				**$509**	**0.067**	**$7,571**
Alternative utility inputs using 10-year time horizon						
Disutility with weight gain[c]		0.00195	CADTH[9,15]	–$332	0.005	Dominant[b]
		0.0061	Bagust et al.[21]		0.009	Dominant[b]
Alternative utility inputs using reduced DPP-4 inhibitor price ($2.25 per tablet)						
Disutility with weight gain[c]		0.00195	CADTH[9,15]	$509	0.005	$108,246
		0.0061	Bagust et al.[21]		0.009	$55,639
Alternative utility inputs using reduced dapagliflozin and DPP-4 inhibitor price ($2.25)						
Disutility with weight gain[c]		0.00195	CADTH[9,15]	–$52	0.005	Dominant[b]
		0.0061	Bagust et al.[21]		0.009	Dominant[b]
Alternative utility inputs using price of DPP-4 inhibitor + MET combination product ($2.54 per day)						
Disutility with weight gain[c]		0.00195	CADTH[9,15]	$354	0.005	$75,303
		0.0061	Bagust et al.[21]		0.009	$38,706

BMI = body mass index; DPP-4 = dipeptidyl-peptidase 4; ICUR = incremental cost-utility ratio; MET = metformin; QALY = quality-adjusted life-year.
[a] Manufacturer base case.
[b] A dominant option is associated with greater health gains and lower total costs.
[c] No utility gain with weight loss was applied.

Issues for consideration

- **Potential for off-label use of dapagliflozin.** The clinical expert for this review indicated potential off-label uses for dapagliflozin in T2DM, as well as other SGLT2 inhibitors, mainly as fourth-line treatments in addition to insulin. The expert also mentioned a rising trend in the use of SGLT2 inhibitors in clinical practice as monotherapies adjunct to diet and exercise, an indication for dapagliflozin for which the manufacturer has not submitted a request for CDR review for listing recommendation. Such utilization patterns are based on the perceived class effect on SGLT2 inhibitors on weight and blood pressure in addition to A1C levels. Increased utilization of SGLT2 inhibitors as monotherapy or as fourth-line treatments is expected to cause significant overall expenditure in the treatment of T2DM.
- **Euglycemic diabetic ketoacidosis with dapagliflozin.** A recent publication described the potential association of SGLT2 inhibitors with euglycemic diabetic ketoacidosis.[22] This AE was not included as part of the AEs assessed in the model's base-case analysis, but only in the sensitivity analysis. Further evidence would be required to appropriately assess the impact of this AE on costs and outcomes in this population.

The availability of dapagliflozin as an alternative treatment option for stabilizing blood glucose was reported as important to patients. Patient input also described lowering SBP to be important and essential. Patients noted the AEs associated with dapagliflozin, such as repeated vaginal yeast infections, urinary tract infections, and constipation while on dapagliflozin. Change in A1C and SBP, as well as urogenital infections and their impact on costs and quality of life were included in the economic model.

Conclusions

The evidence presented by the manufacturer to support the cost-effectiveness of dapagliflozin as a third-line treatment added on to metformin and a sulfonylurea was based on a 10 mg daily dosing. The cost-effectiveness of dapagliflozin 5 mg daily versus other comparators remains unknown.

Results were sensitive to utility values associated with weight changes, comparative pricing of dapagliflozin with DPP-4 inhibitors, and model time horizon. CDR reanalyses assumed equal price for dapagliflozin and DPP-4 inhibitors.

CDR analyses found that the ICUR for dapagliflozin versus DPP-4 inhibitors could be as high as $71,360 per QALY when added to metformin and a sulfonylurea over 40 years. Incremental costs associated with dapagliflozin compared with DPP-4 inhibitors were based on drug costs and the increased risk of urogenital infections, while incremental QALYs were small and driven by benefits of dapagliflozin on weight gain, ranging from 0.01 to 0.02 QALYs over 40 years compared with DPP-4 inhibitors.

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 from the Ontario Drug Benefit 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 NON-INSULIN DRUGS USED IN COMBINATION WITH METFORMIN AND A SULFONYLUREA

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Dapagliflozin (Forxiga)	5 mg 10 mg	tab	[redacted][a]	5 mg or 10 mg daily	[redacted]	[redacted]
SGLT2 inhibitors						
Canagliflozin (Invokana)	100 mg 300 mg	tab	2.6177	100 mg or 300 mg daily	2.62	955
Empagliflozin (Jardiance)	10 mg 25 mg	tab	2.6200[b]	10 mg or 25 mg daily	2.62	955
DPP-4 inhibitors						
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	tab	2.1000[c]	25 mg daily	2.10	767
Linagliptin (Trajenta)	5 mg	tab	2.2500[d] to 2.5500	5 mg daily	2.25 to 2.55	821.25 to 931
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	tab	2.3997 2.8753	5 mg daily	2.88	1,049
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)	12.5/500 mg 12.5/850 mg 12.5/1,000 mg	tab	1.1450[c]	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

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Biguanides						
Metformin	500 mg 850 mg	tab	0.0444 0.0610[e]	500 mg three to four times daily	0.13 to 0.18	49 to 65
GLP-1 receptor agonists						
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/mL)	NA[f]	10 mcg twice daily	5.73[de] 5.27[de]	1,924 to 2,091
Liraglutide (Victoza)	2 x 3 mL 3 x 3 mL	Pre-filled pen inj (6 mg/mL)	136.98[c] 205.47[c]	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 if > 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	0.4204[g]	1 mg to 4 mg daily	0.42	153
Glyburide (generics)	2.5 mg 5.0 mg	tab	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

CDR = CADTH Common Drug Review; DPP-4 = dipeptidyl-peptidase 4; ER = extended release; inj = injection; NA = not available; SGLT2 = sodium-glucose cotransporter 2; tab = tablet.

[a] Manufacturer's submitted price.[4]

[b] Empagliflozin was reviewed by CDR as third-line therapy added on to sulfonylurea and metformin.[23]

[c] Quebec Drug Formulary (RAMQ) (accessed November 2015).[24]

[d] Nova Scotia list price for linagliptin 5 mg tablet (accessed November 2015).[8]

[e] Saskatchewan Drug Formulary (accessed November 2015).[25]

[f] Byetta cost is estimated using data for private plans in Ontario from IMS PharmaStat, using cost/unit and days/unit to determine a cost/day and removing current ODB dispensing fee and mark-up rates.[26]

[g] Newfoundland and Labrador Drug Formulary (accessed July 2015).[27]

Source: Ontario Drug Benefit (accessed November 2015) prices unless otherwise indicated.[17]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 6: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DAPAGLIFLOZIN RELATIVE TO LINAGLIPTIN AS ADD-ON TO METFORMIN AND A SULFONYLUREA?

Dapagliflozin vs. Glyburide	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	Dapagliflozin dominates DPP-4 inhibitors					

CE = cost-effectiveness; DPP-4 = dipeptidyl-peptidase 4; NA = not applicable; vs. = versus.
Note: Based on manufacturer's results.[4]

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: AUTHOR INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH Common Drug Review			
☐ 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: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DAPAGLIFLOZIN

TABLE 9: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	National Institute for Health and Care Excellence[28]
Publication Date	June 2013
Drug	5 mg or 10 mg tablets
Reported Price	£36.59 for 28 5 mg or 10 mg tablets — price per tablet calculated to be £1.30
Treatment	Dapagliflozin is administered orally as a single dose of 10 mg per day
Comparators	Triple therapy with MET + SU: DPP-4 inhibitors, TZDs, and GLP-1 analogues
Population Modelled	Triple therapy for people with T2DM (as add-on to MET + SU)
Time Horizon	40 years
Cycle Length	6 months
Discount Rate	3.5% on both costs and outcomes
Type of Model	CUA: Simulation model with Excel front — main calculations performed using C++ programming.
Key Outcomes	QALYs; life-years; costs
Manufacturer Results	Triple therapy (add-on to MET + SU): • ICER: Dapagliflozin dominated DPP-4 inhibitors, TZDs, and GLP-1 analogues The manufacturer reported the results were sensitive to choice of utility values
Sources of Uncertainty	ERG noted: • DPP-4 inhibitors expected to be used before GLP-1 analogues in triple therapy (cheaper plus oral administration); considered DPP-4 inhibitors key comparators in dual- and triple-therapy settings. • Clinical effectiveness in triple therapy was less robust, although studies in this population were ongoing. • Utility loss associated with hypoglycemic events (Currie et al. 2006) was too large when applied within the model; utility loss should have been applied for 3 months as opposed to 12 months. • QALY gain associated with impact on weight change given data from Study 12 did not match results seen in model based on published utility data (Lane et al.). ERG considered alternate utility values (Bagust et al.). • Should have applied annual in-patient and non–in-patient costs for no diabetic complication (UKPDS 65). • Event probabilities and associated costs were misapplied in the model. • Incorrect implementation of UKPDS risk factor equations in the model. • Baseline values should have been same for all treatment groups.
HTA Agency Results	The Committee noted that in both the manufacturer's original and revised triple-therapy analyses from the assessment group, dapagliflozin dominated other comparator drug therapies.
Recommendation	The Committee considered that the cost-effectiveness analyses should be considered as exploratory in nature, and concluded that dapagliflozin should not be recommended as triple therapy.
CDR Assessment	The economic evaluations appear to be similar in nature; NICE identified similar limitations as CDR.

CDR = Common Drug Review; CUA = cost utility analysis; DPP-4 = dipeptidyl-peptidase 4; ERG = evidence review group; GLP-1 = glucagon-like peptide-1; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; MET = metformin; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione; UKPDS = United Kingdom Prospective Diabetes Study.
Note: £1 = C$2.03 (Bank of Canada, August 12, 2015)

APPENDIX 5: REVIEWER WORKSHEETS

1. Manufacturer's model structure

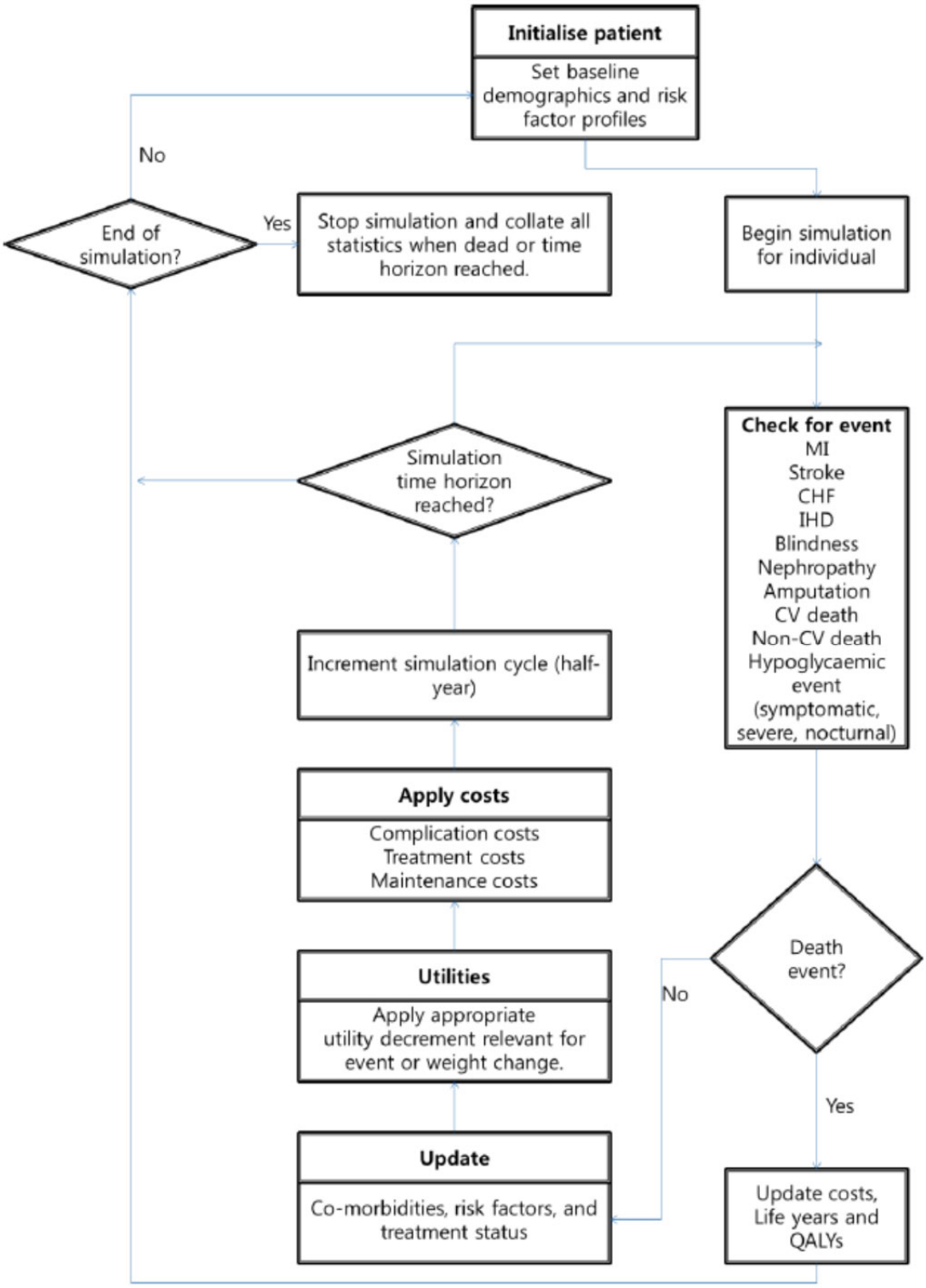
The manufacturer submitted a cost-utility analysis of dapagliflozin as add-on therapy to metformin and a sulfonylurea. When added to metformin and a sulfonylurea, dapagliflozin was compared with a dipeptidyl-peptidase 4 (DPP-4) inhibitor. Efficacy data for the analysis were obtained from a network meta-analysis (NMA). The base-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 Cardiff Diabetes Model.[3]

The Cardiff Diabetes Model is a validated, fixed-time-increment stochastic simulation designed to evaluate the impact of new therapies in a cohort of up to 10,000 hypothetical patients over a period of 40 years.[3] The cohorts of hypothetical patients are defined by a set of characteristics including demographics (e.g., age and gender), biomarker 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 value of these variables changed as the model simulation progressed, as a result of the effects of antidiabetic treatment and through natural progression, calculated from the United Kingdom Prospective Diabetes Study (UKPDS number 68) risk factor equations. Macrovascular events predicted in the model included ischemic heart disease, myocardial infarction (MI), congestive heart failure, and stroke. Microvascular events included amputation, nephropathy (end-stage renal failure) and blindness. The economic model included changes in weight associated with treatment. UKPDS risk equations based on BMI were included in the model. Therefore, changes in patient weight over time were converted to a BMI value based on baseline weight and height characteristics. If a treatment was associated with weight loss, this involved assumptions about how long the weight loss was maintained, along with the subsequent time until the loss of effect and return to baseline body weight.[3]

Simulated patients moved through the model in six-month cycles over a 40-year time horizon. At the start of the model, patients were assumed to have no complications associated with type 2 diabetes mellitus (T2DM). At the end of the first six-month cycle, the UKPDS risk equations determined the probability of fatal and non-fatal complications in addition to diabetes-related deaths (myocardial infarction, congestive heart failure, stroke, and amputation) and deaths from other causes (estimated separately from UK life tables). If patients survived beyond the first cycle, they moved to the next cycle in which they remained at risk of treatment-related adverse events (AEs) and long-term macrovascular or microvascular events. Once a diabetes-related death or death from other causes occurred, then costs, life-years, and quality-adjusted life-years (QALYs) were updated and the simulation ended for that patient (Figure 1).[3]

Standard outputs from model simulations included the incidence of microvascular (retinopathy, neuropathy, or nephropathy) and macrovascular complications (congestive heart disease, MI, sudden death, and cerebrovascular disease defined as neurological deficit with symptoms or signs lasting one month or more), mortality, cost-effectiveness and cost-utility data, and acceptability curves. The model also calculated the probability of drug-related hypoglycemic events (non-severe and severe), other AEs including urinary tract infections and genital infections, and treatment discontinuation caused by AEs.[3]

FIGURE 1: COST-EFFECTIVENESS MODEL STRUCTURE



CHF = congestive heart failure; CV = cardiovascular; IHD = ischemic heart disease; MI = myocardial infarction; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission, Figure 6.1, page 20.[4]

The majority of disutility weights associated with complications of T2DM were obtained from UKPDS 62[10] with the exception of end-stage renal disease (ESRD), which was sourced from a published study by Currie et al.[11]). The health utility of changes in BMI used in the analysis was based on a Canadian study that estimated utilities using a time trade-off utility valuation method for a set of six weight-related T2DM health states from 96 Canadian T2DM patients with a mean age of 55 years and a mean BMI of 32 kg/m^2.[12] The study by Lane et al. showed that for every one unit increase in BMI there was an associated decrease in utility of 0.0472, and for every one unit decrease in BMI, there was an associated increase in utility of 0.0171.[12] Disutility weights associated with hypoglycemia were sourced from the CADTH Optimal Use Report for third-line pharmacotherapy in T2DM.[9,15] Utility decrements related to the occurrence urinary tract infection (UTI) and genital infection were derived from a published economic evaluation of care interventions for UTIs in women.[13]

Unit costs for drugs were obtained from the Ontario Public Drug Program (year not specified).[17] The manufacturer assumed that episodes of mild/moderate hypoglycemia had no impact on health service resource use.[4,15] Costs associated with managing severe hypoglycemic episodes were derived from published reports.[14] Costs associated with managing long-term diabetes-related complications and treating AEs were obtained from published sources.[9,15,16,29]

TABLE 10: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	In the absence of head-to-head trial data, an NMA was used to populate the analyses of dapagliflozin vs. DPP-4 inhibitor in patients on MET + SU.[6]	Uncertain. Several limitations identified with manufacturer NMA: • lack of comparison results by time point (e.g., 24 weeks) • trials of different duration were included • pooling of classes in NMA despite dosage or mode of administration • not all third-line comparators were included.
Natural history	Natural history of T2DM was integrated in the model data from the UKPDS based on data with follow-up time of approximately 30 years.[5]	Appropriate; however, the generalization of the model to a Canadian perspective may be limited.

Utilities	• Disutilities associated with complications of T2DM primarily sourced from UKPDS 62 (Clarke 2002)[10] except for ESRD, which were sourced a study by Currie et al. (2005).[30]
	• Utilities associated with modelled treatment-related AEs and weight change were supplemented from the literature:
	  ○ utilities/disutilities associated with weight change were obtained from a time trade-off study of 96 Canadian patients with T2DM (Lane et al. 2014)[12]
	  ○ disutility weights associated with symptomatic non-severe and severe hypoglycemia events were sourced from CADTH Optimal Use report.[9,15]
	• Disutility associated with AEs derived from a published economic evaluation by Barry et al.
		Likely appropriate for most of these, except for the utilities/ disutilities associated with weight change, which are questionable. Other published sources were tested in sensitivity analyses.[9,15,21]

Data Input	Description of Data Source	Comment
	(1997).[13]	
AEs (Indicate which specific AEs 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.
Mortality	All-cause mortality was estimated using gender-specific life tables for Canada.[31]	Appropriate.
Costs		
Drug	Unit costs for drugs were obtained from the Ontario Public Drug Program when available.[17]	The manufacturer submission did not specify the date of the drug costs.
Event	• Costs associated with managing long-term diabetes-related complications were obtained published sources.[9,15] • Cost of severe hypoglycemia was based on a report by O'Brien et al. (2003).[14]	
AEs	Costs were derived from published sources: • Ontario Ministry of Health[29] • study by Turner et al. (2010).[16]	

AE = adverse event; DPP-4 = dipeptidyl-peptidase 4; ESRD = end-stage renal disease; GMI = genital mycotic infection; MET = metformin; NMA = network meta-analysis; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; UKPDS = United Kingdom Prospective Diabetes Study; UTI = urinary tract infection; vs. = versus.

TABLE 11: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
In the base-case analysis, the delay in creep (how long the effect lasts before A1C begins to rise in line with natural progression) was set to zero for all treatment groups, and the natural A1C progression was equal between treatments.	Likely appropriate.
The base-case analysis assumed that patients on dapagliflozin to experience weight loss during the first year on therapy, which was maintained for one year.	Appropriate.
Patient weight rose by more than the original reduction, as it was assumed that weight would be regained until it was back in line with natural weight progression. Thereafter, the patient's weight increased in accordance with the natural weight progression (0.25 kg per year).	Appropriate.
Mild/moderate hypoglycemic events required no health care resource use and as such, had no associated costs.	Appropriate.
The costs for UTI and genital infection events were assumed to consist of the cost of a visit to the general practitioner. The cost of antibiotics, urine analysis, or other drugs or tests were not included but were assumed to be minimal.	Likely appropriate.
Structural assumptions of the model concerning long-term predictions of complications based on UKPDS 68 were assumed to be valid and were not investigated in scenario or sensitivity analyses.	Appropriate.
Patients were assumed to be 100% compliant with no	Inappropriate.

Assumption	Comment
discontinuations.	Based on progressive nature of diabetes, it is highly probable that some patients will experience a decline in their renal function, which would necessitate discontinuation of dapagliflozin over the model's lifetime duration.
Patients were assumed to have no clinical history of microvascular or macrovascular events.	Likely appropriate. Considered by clinical exert to be representative of overall patients in clinical practice but not all.
There was no treatment effect assumed for any treatment on cholesterol given insufficient data to inform the NMA.	Appropriate
Utilization of UKPDS 68 risk equations. The UKPDS 68 equations comprise of a series of seven Weibull proportional hazards models derived from a cohort of 5,102 diabetic patients, aged 25 to 65 years in the UK from the UKPDS[5] that ran for 20 years (1977 to 1997) for prediction of cardiovascular events.	A review of the UKPDS design reveals that it recruited relatively healthy, newly diagnosed T2DM patients. The generalizability of the results of the UKPDS risk equations to clinical practice may be challenging when applied in patients with more advanced diseases and comorbidities and with the improvements in clinical practice and management of diabetes from the time of the UKPDS itself.[18,19] Also, the generalization of these equations to a Canadian context is questionable.
Assumptions around A1C and cardiovascular events. Since the Cardiff model used equations from the UKPDS 68 outcomes study, it is therefore based on the inherent assumption that reductions in A1C levels are associated with reduced cardiovascular events and improvements in microvascular and macrovascular events.	Such expected benefits have become debatable, as the available evidence shows reduction in microvascular events only in patients with aggressive reductions in A1C,[18] while most guidelines no longer recommend aggressive reductions in A1C for diabetic patients due to potentially increased risk of hypoglycemia.[18,19]
Assumption on weight changes and quality of life. The submitted analysis applied utility increments and decrements to weight loss and gain, respectively, based on the assumption that changes in weight will likely impact quality of life.	Given the structure of the model, this assumption appears to equate weight changes to improvements in clinical outcomes either directly or due to decreased A1C levels; such reductions in weight are modelled to produce reductions in congestive heart failure. No evidence has been identified to associate long-term weight loss with improvements in quality of life,[18-20] and double-counting of this change in quality of life is envisaged considering the model structure, which applies disutility to comorbidities that correlate with weight change.
Modelling of future events. The economic evaluation relied on short-term clinical data (trial duration between 17 to 52 weeks)[4] to model and predict the costs and incidence of complications over a 40-year time horizon.	With the lack of evidence demonstrating that short-term effects can be sustained over the long term, and with the uncertainty over changes in A1C or weight would equate to long-term clinical benefits, the modelling of the costs and incidents over a shorter

Assumption	Comment
	time horizon might be more relevant until more reliable long-term data are available.

A1C = glycated hemoglobin; NMA = network meta-analysis; T2DM = type 2 diabetes mellitus; UKPDS = United Kingdom Prospective Diabetes Study; UTI = urinary tract infection.

4. Manufacturer's additional analyses

In the base case (i.e., dapagliflozin compared with DPP-4 inhibitor as an add-on to metformin and a sulfonylurea), the manufacturer reported that dapagliflozin dominated DPP-4 inhibitors (less costly, more effective).

The manufacturer conducted a scenario analysis assessing the cost-effectiveness of dapagliflozin compared to insulin (neutral protamine Hagedorn) based on the efficacy results of the NMA. Considering the listing requested for dapagliflozin added to metformin and a sulfonylurea is for patients for whom insulin is not an option, this scenario analysis is, in context, superfluous. Nevertheless, insulin was reported as the cost-effective option in the CADTH Optimal Use report on third-line treatments for T2DM when compared with DPP-4 inhibitors and glucagon-like peptide-1 (GLP-1) analogues.[9] The result of the scenario analysis reported dapagliflozin dominating insulin (less costly, more effective) (Table 12).

TABLE 12: MANUFACTURER'S SCENARIO ANALYSIS RESULTS

	MET + SU + dapagliflozin	MET + SU + insulin	Difference
Costs			
Drug treatment (total)	$13,366.64	$13,686.01	–$319.37
Severe hypoglycemia	$1.21	$1.14	$0.07
Other AE (UTI, genital infection)	$137.98	$33.25	$104.74
IHD	$2,573.08	$2,572.22	$0.86
MI	$3,953.24	$3,978.58	–$25.34
Stroke	$2,524.24	$2,568.78	–$44.54
CHF	$2,841.39	$2,848.08	–$6.69
Blindness	$905.44	$887.16	$18.28
Nephropathy	$1,742.01	$1,794.61	–$52.60
Amputation	$2,563.23	$2,536.76	$26.47
Total	**$30,608.47**	**$30,906.61**	**–$298.14**
QALYs	**10.692**	**10.205**	**0.488**
ICUR			**Dominant[a]**

AE = adverse event; CHF = congestive heart failure; ICUR = incremental cost-utility ratio; IHD = ischemic heart disease; MET = metformin; MI = myocardial infarction; QALY = quality-adjusted life-year; SU = sulfonylurea; UTI = urinary tract infection.
[a] A dominant option is associated with greater health gains and lower total costs.
Source: Adapted from manufacturer's pharmacoeconomic submission, Tables 7.6 and 7.8 (pages 51-53).[4]

Probabilistic sensitivity analysis

The manufacturer conducted the probabilistic sensitivity analysis (PSA) by simulating 1,000 cohorts of 1,000 patients in which values of key parameters were drawn randomly and independently from the parameter distributions. Standard errors (SE) were used for the parameter distribution if available; otherwise, the manufacturer assumed the SE to be 20% of the mean, except for costs where the SE was assumed to be 10%.[4] Beta distributions were used for utilities and probability estimates, gamma distributions were used for costs, and normal distributions were used for the other parameters.[4] The cost-effectiveness acceptability curves indicate that dapagliflozin had a 55% likelihood of being cost-effective versus DPP-4 inhibitors when added to metformin and a sulfonylurea at a threshold of $10,000 per QALY. A PSA was not conducted using the scenario analysis of dapagliflozin compared with insulin when added to metformin and a sulfonylurea.

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