Common Drug Review
Pharmacoeconomic Review Report

June 2016

Drug	Dulaglutide (Trulicity)
Indication	For the once-weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with: • diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance. • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control. • prandial insulin with metformin, when diet and exercise plus basal or basal-bolus insulin therapy (up to two injections of basal or basal plus prandial insulin per day) with or without oral antihyperglycemic medications do not achieve adequate glycemic control
Reimbursement request	For the once-weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with: • metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.
Dosage form(s)	0.75 mg and 1.5 mg (subcutaneous injection, once-weekly)
NOC date	November 10, 2015
Manufacturer	Eli Lilly Canada Inc.

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

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ABBREVIATIONS

BMI	body mass index
CDR	CADTH Common Drug Review
CUA	cost-utility analysis
DPP-4	dipeptidyl peptidase-4
GLP-1	glucagon-like peptide-1
A1C	glycated hemoglobin
ICUR	incremental cost-utility ratio
NMA	network meta-analysis
OU	optimal use
QALY	quality-adjusted life-year
SGLT2	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	**Dulaglutide 0.75 and 1.5 mg**
Study Question	To assess the cost-effectiveness of dulaglutide 0.75 mg and 1.5 mg as add-on therapy to metformin alone or metformin plus a sulfonylurea in a Canadian population of T2DM patients.
Type of Economic Evaluation	CUA
Target Population	Adult patients with T2DM who have inadequate glycemic control on: • metformin (second-line therapy) • metformin plus a sulfonylurea (third-line therapy)
Treatment	Dulaglutide 0.75 mg or 1.5 mg once weekly, administered subcutaneously
Outcome	QALYs
Comparators	Second-line setting (add-on to metformin): • Sulfonylurea (gliclazide 80 mg daily) • Basal insulin (insulin glargine 0.53 IU/kg/day) • Biphasic insulin (insulin lispro/insulin lispro protamine 1.5 IU/kg/day) • GLP-1 analogues (as a class, based on NMA data) • Liraglutide (1.58 mg mean daily dose, based on direct comparison with dulaglutide 1.5 mg) Third-line setting (add-on to metformin plus a sulfonylurea): • Insulin glargine (0.53 IU/kg/day) • Biphasic insulin (insulin lispro/insulin lispro protamine 1.5 IU/kg/day) • GLP-1 analogues (liraglutide 1.58 mg mean daily dose)
Perspective	Canadian ministry of health
Time Horizon	Lifetime (up to 40 years)
Results for Base Case	ICUR for dulaglutide as second-line therapy compared with: • Basal insulin: $126,049 per QALY (0.75 mg) and $104,402 per QALY (1.5 mg) • Biphasic insulin: $9,101 per QALY (0.75 mg) and $9,356 per QALY (1.5 mg) • GLP-1 class: dulaglutide (both doses) less costly and less effective than GLP-1s • Liraglutide: dulaglutide 1.5 mg dominated (less costly, more effective) liraglutide • Sulfonylurea: $185,013 per QALY (0.75 mg) and $165,971 (1.5 mg) ICURs for dulaglutide as third-line therapy compared with: • Basal insulin: $66,674 per QALY (0.75 mg) and $56,016 per QALY (1.5 mg) • Biphasic insulin: $10,820 per QALY (0.75 mg) and $11,740 per QALY (1.5 mg) • GLP-1: dulaglutide (0.75 mg and 1.5 mg) dominated (less costly, more effective) GLP-1 analogues
Key Limitations	CDR identified the following key limitations with the submitted economic analysis: • Comparison with GLP-1 analogues: The most appropriate type of evaluation for dulaglutide versus other GLP-1 analogues is a cost-minimization, rather than cost-utility, analysis, given the lack of differences in clinical outcomes in the manufacturer-submitted NMA. Also, a lower publicly available price of liraglutide than the value used by the manufacturer was identified. • Uncertainty in utility values: There is uncertainty regarding the most appropriate disutility associated with increased BMI. The manufacturer used a higher value than previous CADTH analyses of second- and third-line diabetes therapies. The manufacturer also applied a disutility to SMBG derived from an unspecified source that was of uncertain validity.

	• Choice of basal insulin: The manufacturer compared dulaglutide with insulin glargine, but the CADTH recommendations for third-line therapy recommend insulin NPH, with the long-acting analogues recommended as an option if the price is similar to that of insulin NPH. Furthermore, some CDR-participating jurisdictions reimburse insulin glargine on a restricted basis. Therefore, insulin NPH is a relevant comparator to dulaglutide in the analysis of third-line therapy. • Orally administered comparators: Dulaglutide was assumed to primarily replace other injectable therapies (i.e., insulin regimens and GLP-1 analogues); consequently, most oral comparators were excluded from the analyses. CDR considered oral alternatives to be relevant comparators. • Baseline characteristics: In the second-line analysis, baseline prevalence of complications in the technical model reflected the third-line treatment population, and was not based on the CADTH second-line report, as stated by the manufacturer.
CDR Base-Case Estimate(s)	CDR's base-case analyses for second- and third-line therapy addressed the identified limitations by revising the price of liraglutide, using the disutility for weight gain employed in previous CADTH reports, revising the baseline prevalence of complications in the second-line analysis, and incorporating DPP-4 inhibitors and SGLT2 inhibitors. According to CDR's base-case analyses, dulaglutide was only likely to be cost-effective at conventional thresholds compared with biphasic insulin. The CDR base-case ICURs for dulaglutide for second-line therapy were as follows: • $293,000 to $512,000 per QALY compared with basal insulin • Approximately $13,000 per QALY compared with biphasic insulins • $245,000 to $278,000 per QALY compared with sulfonylureas • $741,000 to $1.5 million per QALY compared with DPP-4 inhibitors • $871,000 to $2.6 million per QALY compared with SGLT2 inhibitors. The CDR base-case ICURs for dulaglutide for third-line therapy were as follows: • $123,000 to $182,000 per QALY compared with insulin glargine • Approximately $29,000 per QALY compared with biphasic insulins • $304,000 to $468,000 per QALY compared with DPP-4 inhibitors • $423,000 to $846,000 per QALY compared with SGLT2 inhibitors. In comparison with GLP-1 analogues, dulaglutide is more costly than liraglutide (5.5% more) at the mean dose of 1.58 mg/day referenced in the manufacturer's analysis, but costs the same as liraglutide 1.8 mg/day. Dulaglutide is more costly than exenatide 10 mcg twice daily (71.6% more), but costs the same as weekly exenatide (2 mg/week).

BMI = body mass index; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; 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; SGLT2 = sodium/glucose cotransporter 2; SMBG = self-monitoring of blood glucose; T2DM = type 2 diabetes mellitus.

EXECUTIVE SUMMARY

Background

Dulaglutide (Trulicity) is a long-acting human glucagon-like peptide-1 (GLP-1) receptor analogue that is administered subcutaneously once weekly. Dulaglutide was submitted to the CADTH Common Drug Review (CDR) for the treatment of patients with type 2 diabetes mellitus (T2DM):

1) In combination with metformin when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control
2) In combination with metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.

The recommended starting dose of dulaglutide is 0.75 mg once weekly, administered subcutaneously. The dose may be increased to 1.5 mg once weekly for additional glycemic control.[1] The maximum recommended dose is 1.5 mg once weekly.[1] The manufacturer submitted a market list price of $47.95 per single-use pre-filled pen for dulaglutide 0.75 mg and 1.5 mg.[2]

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted cost-utility analyses (CUAs) of dulaglutide as add-on therapy to metformin or metformin plus a sulfonylurea in patients with T2DM using the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model. The analyses were conducted from the perspective of a provincial health ministry over a 40-year time horizon, and a discount rate of 5% was applied.[3,4] The following analyses were reported:

- For dulaglutide in combination with metformin (i.e., second-line therapy), dulaglutide 0.75 mg and 1.5 mg were compared with sulfonylureas, basal insulin, biphasic insulin, and the glucagon-like peptide-1 (GLP-1) analogues as a class using results from a network meta-analysis (NMA) of second-line therapies. A second analysis compared dulaglutide 1.5 mg with liraglutide 1.8 mg using clinical data from the AWARD-6 trial.[5]
- For dulaglutide in combination with metformin plus a sulfonylurea (i.e., third-line therapy), dulaglutide 0.75 mg and 1.5 mg were compared with insulin glargine, biphasic insulins, and other GLP-1 analogues using results from an NMA on third-line pharmacotherapies. In a second analysis, dulaglutide 0.75 mg and 1.5 mg were compared with insulin glargine using clinical data from the AWARD-2 trial.[6]

In the second-line setting, dulaglutide 0.75 mg and 1.5 mg resulted in incremental cost-utility ratios (ICURs) of between $104,402 and $126,049 per QALY compared with basal insulin; $9,101 and $9,356 per quality-adjusted life-year (QALY) gained compared with biphasic insulin; and $165,971 and $185,013 per QALY compared with a sulfonylurea. Compared with other GLP-1 analogues, dulaglutide was less effective and associated with lower costs based on the results of the NMA. However, when the analysis was based on clinical data from the AWARD-6 trial, dulaglutide 1.5 mg dominated (i.e., was less costly and more effective) liraglutide 1.8 mg.

In the third-line setting, ICURs for dulaglutide were between $56,057 and $62,152 per QALY compared with insulin glargine, and $10,820 and $11,740 per QALY compared with biphasic insulins. Dulaglutide was dominant (i.e., less costly and more effective) when compared with GLP-1 analogues as a class. When the analysis was based on clinical data from the AWARD-2 trial, dulaglutide resulted in an ICUR of $56,016 to $66,674 per QALY compared with insulin glargine.

Sensitivity analyses conducted by the manufacturer indicated that the results were most sensitive to the treatment effect of dulaglutide on glycated hemoglobin (A1C) and body mass index (BMI), and the choice of utilities associated with hypoglycemic events, self-monitoring of blood glucose (SMBG), and changes in BMI.

Summary of Identified Limitations and Key Results

CDR identified the following key limitations with the submitted economic analysis:

- **Comparison with GLP-1 analogues:** Other GLP-1 analogues were not considered a policy-relevant comparator for dulaglutide, as these drugs are currently not listed by CDR-participating jurisdictions. Furthermore, the most appropriate type of evaluation of dulaglutide versus other GLP-1 analogues is a cost-minimization, rather than cost-utility, analysis, given the lack of differences in clinical outcomes in the manufacturer-submitted NMA. Finally, a lower publicly available price of liraglutide than the value used by the manufacturer was identified.
- **Uncertainty in utility values:** There is uncertainty regarding the most appropriate disutility associated with increased BMI. The manufacturer used a higher value than CADTH's Optimal Use (OU) reports on second- and third-line therapy. The manufacturer also applied a disutility to SMBG derived from an unspecified source that was of uncertain validity.
- **Choice of basal insulin:** The manufacturer compared dulaglutide with insulin glargine; however, the CADTH OU recommendations for third-line therapy recommend insulin NPH, with the long-acting analogues recommended as an option if the price is similar to that of insulin NPH. Furthermore, some CDR-participating jurisdictions list insulin glargine on a restricted basis. Therefore, insulin NPH is a relevant comparator to dulaglutide in the analysis of third-line therapy.
- **Orally administered comparators**: Dulaglutide was assumed to primarily replace other injectable therapies (i.e., insulin regimens and GLP-1 analogues); consequently, most oral comparators were excluded from the analyses. CDR considered oral alternatives to be relevant comparators.
- **Baseline characteristics**: The baseline prevalence of complications in the manufacturer's analysis of second-line therapy was reportedly derived from the CADTH OU report on second-line therapy, when in fact the model was found to incorporate several values from the AWARD-2 trial of third-line therapy. As well, inconsistencies were found between the second- and third-line analyses in the baseline prevalence of some complications; e.g., the prevalence of prior myocardial infarction (MI) was 9% in the second-line analysis, but only 3% in the third-line analysis.

The CDR base-case analyses addressed the above limitations as follows:

- A reduced liraglutide cost of $6.49 per day was applied based on a publicly available price (Quebec drug benefit list, February 2016)[7] and the mean dose used by the manufacturer in the analysis.
- The disutility for increases in body weight was revised to reflect the value used in previous CADTH OU reports on second- and third-line therapy. The disutility associated with SMBG was removed.
    - Using efficacy data from the manufacturer-submitted NMAs for second- and third-line therapies, CDR conducted scenario analyses that compared dulaglutide 0.75 mg and 1.5 mg to dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin, $2.25/day)[8] and sodium/glucose cotransporter 2 (SGLT2) inhibitors (dapagliflozin, $2.45/day)[7] in the second- and third-line therapy settings.
- The baseline prevalence of complications in the second-line analysis was revised to reflect the CADTH OU report for second-line therapy.

The CDR base-case ICURs for dulaglutide as second-line therapy were as follows:

- $293,000 to $512,000 per QALY compared with basal insulin

- Approximately $13,000 per QALY compared with biphasic insulins
- $245,000 to $278,000 per QALY compared with sulfonylureas
- $741,000 to $1.5 million per QALY compared with DPP-4 inhibitors
- $871,000 to $2.6 million per QALY compared with SGLT2 inhibitors.

The CDR base-case ICURs for dulaglutide as third-line therapy were as follows:

- $123,000 to $182,000 per QALY compared with insulin glargine
- Approximately $29,000 per QALY compared with biphasic insulins
- $304,000 to $468,000 per QALY compared with DPP-4 inhibitors
- $423,000 to $846,000 per QALY compared with SGLT2 inhibitors.

In comparison with GLP-1 analogues, dulaglutide is 5.5% more costly than liraglutide at the mean dose of 1.58 mg/day referenced by the manufacturer, but the same cost as liraglutide 1.8 mg/day. Dulaglutide is 71.6% more costly than exenatide 10 mcg twice daily, but the same cost as weekly exenatide (2 mg/week).

CDR also performed a scenario analysis to examine the effect of including insulin NPH as a comparator, based on a cost per 10 mL vial (Novolin ge NPH 100 U/mL) of $22.56 (Ontario Drug Benefit, 2016).[9] This analysis was based on the manufacturer's base case, and an assumption of equivalent clinical outcomes between insulin NPH and insulin glargine. The ICURs for dulaglutide versus insulin NPH were between $170,000 and $207,000 per QALY in the analysis of second-line therapy, and $80,000 and $96,000 per QALY in the analysis of third-line therapy.

CDR noted that a subsequent entry biologic (SEB) of insulin glargine, Basaglar, was recently approved by Health Canada and is available at a price 15% lower than that of the list price for the reference product (Lantus).[10] Basaglar is currently under review by CDR.

Conclusions

According to CDR's base-case analyses for second- and third-line therapy, dulaglutide was likely to be cost-effective only at conventional thresholds compared with biphasic insulin. Dulaglutide was unlikely to be cost-effective compared with basal insulin (insulin glargine) for either second-line therapy in combination with metformin, or third-line therapy in combination with metformin plus a sulfonylurea. Price reductions of 25% or more would be required according to the CDR base case for dulaglutide to be considered cost-effective versus insulin glargine, with larger reductions required in comparison with insulin NPH and SEB insulin glargine.

For second-line therapy compared with sulfonylureas, and for second- and third-line therapy compared with DPP-4 inhibitors or SGLT2 inhibitors, dulaglutide was associated with high ICURs (> $200,000/QALY) in CDR's base-case analyses. Dulaglutide price reductions of 50% or more would be required for ICURs to fall in a range that may be considered cost-effective in comparison with these drugs.

A cost-minimization analysis was considered sufficient for the comparison of dulaglutide with other GLP-1 analogues as the manufacturer's indirect comparison reported no significant differences in efficacy or safety. At the submitted price, dulaglutide is more costly than liraglutide (based on the mean dose referenced by the manufacturer) and daily exenatide (price reductions of 5.5% and 71.6%, respectively, are required for price parity), and the same cost as weekly exenatide.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis (CUA) of dulaglutide as add-on therapy to metformin or metformin plus a sulfonylurea. When added to metformin, dulaglutide was compared to glucagon-like peptide-1 (GLP-1) receptor analogues, insulin glargine, biphasic insulin, and sulfonylurea. For analyses of dulaglutide as add-on therapy to metformin plus a sulfonylurea, dulaglutide was compared with insulin glargine, biphasic insulin, and GLP-1 receptor analogues. The analyses were conducted from the perspective of a provincial health ministry over a 40-year time horizon. Future costs and effects were discounted at a rate of 5%.[3,4]

The CUAs were conducted using the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model; a discrete event simulation model based on data from the UKPDS that predicts long-term diabetes-related complications based on patient characteristics and glycated hemoglobin (A1C) levels. The UKPDS was a large-scale randomized clinical trial that evaluated strategies for intensive blood glucose and blood pressure control.[11]

Efficacy data for dulaglutide 1.5 mg compared with liraglutide 1.8 mg as add-on to metformin were obtained from the AWARD-6 trial, an open-label, 26-week, active-controlled, phase 3 non-inferiority trial that enrolled participants with type 2 diabetes mellitus (T2DM) with inadequate glycemic control on metformin alone.[5,12] Participants were randomized (1:1) to receive subcutaneously injected once-weekly dulaglutide 1.5 mg or subcutaneously injected once-daily liraglutide 1.8 mg. Analyses of dulaglutide 0.75 mg and 1.5 mg compared with sulfonylureas, GLP-1 analogues as a class, and basal and biphasic insulin as add-on to metformin were based on a manufacturer-submitted network meta-analysis (NMA) of second-line therapies that included 51 trials (including AWARD-6) of 27 different treatments that also included dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium/glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, and alpha-glucosidase inhibitors.[2]

For the analyses of dulaglutide 0.75 mg and 1.5 mg compared with insulin glargine as add-on to metformin plus a sulfonylurea, efficacy data were based on the AWARD-2 trial, an open-label, 78-week, active-controlled, phase 3 non-inferiority trial that enrolled participants with T2DM with inadequate glycemic control on metformin plus a sulfonylurea.[6,12] Participants were randomized (1:1:1) to receive subcutaneously injected once-weekly dulaglutide 0.75 mg, dulaglutide 1.5 mg, or once-daily insulin glargine. Analyses of dulaglutide 0.75 mg and 1.5 mg compared with biphasic insulin and GLP-1 analogues were based on a manufacturer-submitted NMA of third-line therapies that included 29 trials (including AWARD-2) of 13 treatments that also included DPP-4 inhibitors, SGLT2 inhibitors, and thiazolidinediones.[2]

The majority of disutility weights associated with complications of T2DM were obtained from the CADTH Optimal Use (OU) reports on second- and third-line treatments for T2DM.[13,14] The utility of changes in body mass index (BMI) used in the analysis was based on a study by Bagust and Beale (2005) that reported a disutility of 0.0061 for every unit of BMI above 25 kg/m^2.[15] Disutility weights associated with hypoglycemia were sourced from a published Canadian study by Harris et al. (2004) that employed a time trade-off approach to estimate the disutility values associated with non-severe and severe

hypoglycemic events.[16] A disutility was applied for self-monitoring of blood glucose (SMBG) testing based on a submission to the Scottish Medicines Consortium for insulin degludec.[17]

Treatment-specific rates of overall hypoglycemia in the second-line setting were derived by multiplying the rate of non-severe hypoglycemia observed in a large trial of insulin glargine for dysglycemia (ORIGIN) by the rate ratios for overall hypoglycemia from the CADTH NMA of second-line therapies.[13,18] For third-line treatment, the event rates for non-severe and severe hypoglycemia were based on data from the AWARD-2 trial.[6,12] The manufacturer assumed that episodes of mild or moderate hypoglycemia had no impact on health care resource use.[3,4] Costs associated with managing severe hypoglycemic episodes, long-term diabetes-related complications, and adverse events were derived from the CADTH reports on second- and third-line therapy for T2DM, adjusted for inflation to 2014 costs.[13,14]

Similar to the CADTH reports on second- and third-line therapy for T2DM,[13,14] all patients in the model were assumed to experience a gradual increase in A1C over time. Therapy was intensified with the addition of insulin NPH when an individual patient's A1C reached 9%.

2. MANUFACTURER'S BASE CASE

The manufacturer's base-case results for dulaglutide as add-on treatment to metformin and metformin plus a sulfonylurea (i.e., second-line and third-line therapy) in patients with T2DM are summarized in Table 2.

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

Base-Case Scenario	Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
Second-Line Therapy			
Dulaglutide 1.5 mg vs. liraglutide 1.8 mg based on AWARD-6[a]	–1,811	0.01	dulaglutide dominant
Dulaglutide 0.75 mg vs. sulfonylurea (gliclazide) based on NMA	29,993	0.16	185,013
Dulaglutide 1.5 mg vs. sulfonylurea (gliclazide) based on NMA	30,449	0.18	165,971
Dulaglutide 0.75 mg vs. GLP-1 analogue class based on NMA	–2,263	-0.03	dulaglutide less expensive, less effective
Dulaglutide 1.5 mg vs. GLP-1 analogue class based on NMA	–1,806	-0.005	dulaglutide less expensive, less effective
Dulaglutide 0.75 mg vs. basal insulin (insulin glargine) based on NMA	13,636	0.11	126,049
Dulaglutide 1.5 mg vs. basal insulin (insulin glargine) based on NMA	13,953	0.13	104,402
Dulaglutide 0.75 mg vs. biphasic insulin based on NMA	2,828	0.31	9,101
Dulaglutide 1.5 mg vs. biphasic insulin based on NMA	3,145	0.34	9,356
Third-Line Therapy			
Dulaglutide 0.75 mg vs. insulin glargine based on AWARD-2	14,120	0.21	66,674

Base-Case Scenario	Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
Dulaglutide 1.5 mg vs. insulin glargine based on AWARD-2	15,100	0.27	56,016
Dulaglutide 0.75 mg vs. insulin glargine based on NMA	11,537	0.19	62,152
Dulaglutide 1.5 mg vs. insulin glargine based on NMA	12,271	0.22	56,057
Dulaglutide 0.75 mg vs. biphasic insulin based on NMA	2,731	0.25	10,820
Dulaglutide 1.5 mg vs. biphasic insulin based on NMA	3,394	0.29	11,740
Dulaglutide 0.75 mg vs. GLP-1 analogue class based on NMA	–806	0.05	GLP-1 dominated by dulaglutide
Dulaglutide 1.5 mg vs. GLP-1 analogue class based on NMA	–143	0.09	GLP-1 dominated by dulaglutide

GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year; vs. - versus.
[a] Dulaglutide 0.75 mg was not studied in the AWARD-6 trial.[2]
Source: Adapted from manufacturer submissions.[3,4]

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Sensitivity analyses were conducted by the manufacturer regarding the results of dulaglutide compared with insulin glargine in the third-line setting, using efficacy data from both the AWARD-2 trial and NMA. The results were most sensitive to the inclusion of A1C and BMI treatment effects in the dulaglutide arm, and the choice (and use) of utilities associated with hypoglycemic events, SMBG testing, and excess BMI. No sensitivity analyses were presented for dulaglutide versus any of the comparators in the second-line setting, or for dulaglutide versus GLP-1 analogues or biphasic insulin in the third-line setting.

Due to technical limitations of the submitted model, the CADTH Common Drug Review (CDR) was unable to recreate the manufacturer's cost-effectiveness acceptability curves or obtain the precise probabilities for dulaglutide in second- or third-line therapy. Therefore, CDR derived the probabilities of dulaglutide being cost-effective at willingness-to-pay thresholds of $50,000 and $100,000 per quality-adjusted life-year (QALY) from the figures provided in the manufacturer's submission:

- At second-line, the probability that dulaglutide was cost-effective at thresholds of $50,000 and $100,000 per QALY compared with sulfonylureas ranged from 0% to 5%.
- Compared with GLP-1 analogues as a class or liraglutide, the probability that dulaglutide was cost-effective as second-line therapy at willingness-to-pay thresholds of $50,000 or $100,000 per QALY ranged from 46% to 95%. The probabilities for dulaglutide versus GLP-1 analogues as third-line therapy ranged from 85% to 92%.
- For dulaglutide compared with basal insulin for second-line therapy, the probability that dulaglutide 0.75 mg and 1.5 mg were cost-effective was 0% and 1%, respectively, at $50,000 per QALY, and 1% and 20%, respectively, at $100,000 per QALY. Compared with insulin glargine in the third-line setting (based on clinical inputs from AWARD-2), the probability that dulaglutide 0.75 mg and 1.5 mg were cost-effective at a threshold of $50,000 per QALY was 12% and 91%, respectively, and 26% and 94%, respectively, at $100,000 per QALY.
- Dulaglutide 0.75 mg and 1.5 mg had the highest probability of being cost-effective at $50,000 and $100,000 per QALY when compared with biphasic insulin in both the second- and third-line settings (100%).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Comparison with GLP-1 analogues

The manufacturer's submissions for second-line and third-line treatments are based on the comparison of dulaglutide with other GLP-1 analogues and insulins.

The following limitations were identified for the comparison with other GLP-1 analogues:

- **Relevance:** GLP-1 analogues are not a policy-relevant comparator, as none of the GLP-1 analogues available in Canada are reimbursed by a CDR-participating jurisdiction.
- **Price:** The manufacturer's analyses for both second-line and third-line settings included a mean daily dose of liraglutide of 1.58 mg at a total daily cost of $7.82 (drug cost of $7.24 plus an 8% markup), based on a unit cost of $82.50 per 18 mg multi-dose pen of liraglutide. The source of the manufacturer's cost for liraglutide was not provided in the submission.
- **Type of evaluation:** The manufacturer conducted a CUA comparing dulaglutide with other GLP-1 analogues in second-line therapy based on efficacy and safety inputs from the AWARD-6 trial and a manufacturer-submitted NMA. However, a cost-minimization analysis comparing dulaglutide with other GLP-1 analogues would have been sufficient (and more easily interpreted) because there were no statistically significant differences between dulaglutide and other GLP-1 analogues on A1C and body weight. The appropriateness of a CUA is further supported by the minimal difference between treatments in total QALYs (e.g., difference of 0.1 QALYs in second-line analysis).

Uncertainty in utility values

- **Changes in BMI:** The manufacturer's model applied a utility reduction of 0.0061 per 1 unit increase in BMI above 25 kg/m^2 based on the publication by Bagust et al. (2005), which was a manufacturer-funded study.[15] There is no evidence to associate long-term weight loss with improvements in clinical outcomes or quality of life,[19-21] and the effect of weight gain on quality of life is subjective and likely to affect individual patients differently. Therefore, the reliability and generalizability of the results of Bagust et al. warrant caution in their interpretation. Furthermore, the previous CADTH OU report on therapies for T2DM incorporated smaller disutility values associated with weight gain (–0.00195 per unit increase in BMI) than those reported by Bagust et al.[13,14]
- **Self-monitoring of blood glucose: The manufacturer's analysis applied a disutility with each weekly SMBG test.** The disutility was based on an unspecified study that was reported in a submission to the Scottish Medicines Consortium (SMC) for insulin degludec.[17] Although the manufacturer did provide the value of the disutility (–0.0058) and how it was converted to a weekly disutility, any information on how the disutility was elicited, calculated, and validated was not provided, thus raising uncertainty over the appropriateness of including the disutility for SMBG testing.

Double-counting

Application of a utility weight to changes in BMI can raise concerns regarding double-counting of benefits from weight-neutral or weight-reducing therapies, as some of the long-term complications in the model correlate with weight changes. This was addressed in the analysis of second-line therapy by setting the model to exclude the effect of BMI as a clinical driver of complications. However, in assessing the analyses of third-line therapy that compared dulaglutide to insulin glargine based on efficacy data from the AWARD-2 trial, CDR noted that the model was in fact set to include the effects of BMI as a driver of clinical complications (i.e., the model was double-counting the effects of increases in BMI).

Comparators

- **Choice of insulin:** The manufacturer compared dulaglutide with insulin glargine under the rationale that insulin glargine has a greater share of the market for basal insulins than insulin NPH. However, the CADTH OU recommendations for third-line therapy recommend insulin NPH, with the long-acting analogues recommended as an option if the price is similar to that of insulin NPH.[22] Furthermore, in some CDR-participating jurisdictions, reimbursement of insulin glargine is restricted to patients who meet certain clinical criteria. Therefore, insulin NPH, which is 63% less costly per unit than insulin glargine, is a relevant comparator to dulaglutide in the analysis of third-line therapy.
- **Oral versus injectable:** The manufacturer assumed that patients with T2DM would prefer oral therapies over injectable; consequently, dulaglutide was assumed to primarily replace other injectable therapies (i.e., insulin regimens and GLP-1 analogues). Therefore, oral comparators to dulaglutide as second-line or third-line treatments were excluded from the analyses, except for sulfonylurea as second-line therapy. The clinical expert consulted by CDR considered this assumption to be appropriate in most situations, while noting the possibility that some patients may opt to replace daily oral treatments with a once-weekly injectable drug such as dulaglutide, for the sake of convenience. In this case, oral therapies may be appropriate comparators for dulaglutide.

Prevalence of complications at baseline

- In the submitted technical model for second-line therapy, the proportion of patients at baseline with a history of diabetes-related complications was taken predominantly from the AWARD-2 trial that studied dulaglutide as a third-line treatment, not the CADTH OU report, as indicated in the manufacturer's report.
- The baseline prevalence of some serious complications was lower in the manufacturer's third-line analysis compared with the values reportedly (but not actually) used in the manufacturer's second-line analysis: atrial fibrillation 1.2% versus 4%, ischemic heart disease 1.1% versus 11.1%, congestive heart failure 0.5% versus 7%, stroke 0.9% versus 5%, and myocardial infarction 3% versus 9%. These discrepancies occurred because some of the prevalence estimates in the manufacturer's third-line analysis were obtained from the AWARD-2 trial rather than the CADTH OU reports. It is not clinically plausible that the prevalence of complications would be lower in a population requiring third-line therapy.

Uncertainty regarding long-term effectiveness

There is uncertainty regarding the long-term efficacy of compared treatments, as improvements in outcomes such as A1C, systolic blood pressure (SBP), and BMI are based on trials of relatively short duration. Furthermore, evidence is emerging that some antidiabetic drugs reduce the risk of cardiovascular events in patients with T2DM,[23] while others do not.[24] This calls into question the validity of results from models of T2DM, like the UKPDS, in which the risk of cardiovascular outcomes is driven entirely by baseline characteristics and surrogate markers such as A1C and BMI, although CDR acknowledges that there are currently no viable alternatives to this approach.

Modelling of adverse events

Based on results from the AWARD trials for dulaglutide, gastrointestinal disorders were the most commonly reported adverse event. However, the economic models for dulaglutide in second-line and third-line settings did not include the impact of gastrointestinal disorders on treatment discontinuations or total costs and outcomes in the analysis.

5. CADTH COMMON DRUG REVIEW REANALYSES

CDR was able to address some of the above limitations, as follows:

- **Prevalence of complications at baseline:** In CDR reanalyses, the baseline complication prevalence estimates for second-line therapy were revised to reflect the values in the CADTH OU report. This reanalysis did not address the issue of inconsistent prevalence estimates between the second- and third-line analyses. However, when CDR ran a scenario analysis in which the baseline prevalence estimates in the third-line analysis were assumed to be the same as in the CDR reanalysis of second-line therapy (data not reported), there was minimal impact on the ICURs. Hence, the manufacturer's prevalence estimates for the third-line analysis were considered appropriate for the CDR base-case analysis of third-line therapy.
- **Cost of liraglutide 1.8 mg:** CDR conducted reanalyses using a liraglutide cost (including an 8% markup) of $6.49 for a mean dose of 1.58 mg daily, based on a publicly available cost of $68.49 per 18 mg multi-dose pen of liraglutide (Quebec drug benefit list, February 2016).[7] The results showed that dulaglutide became a more costly option than liraglutide and GLP-1 analogues as a class (as the price of liraglutide was also used for the latter).
- **Cost-minimization analysis versus GLP-1 analogues:** As described above, a cost-minimization analysis of dulaglutide versus other GLP-1 analogues would have been appropriate, given the lack of significant differences in clinical outcomes reported in the manufacturer's NMA. Based on the submitted price for dulaglutide and publicly available prices for the other GLP-1 analogues (Table 7), dulaglutide is:
  - 5.5% more costly than liraglutide at the mean dose of 1.58 mg/day referenced by the manufacturer, but the same cost as liraglutide 1.8 mg/day
  - 71.6% more costly than exenatide 10 mcg twice daily, but the same cost as weekly exenatide (2 mg/week).
- **Utilities associated with changes in BMI:** The manufacturer's base-case analyses applied utility decrements associated with weight gain from the study by Bagust et al. (2005),[15] although sensitivity analyses removing the disutility associated with weight gain were also reported. Due to the uncertainty in this area, CDR reanalyses were conducted that used disutility values from the previous CADTH OU reports (–0.00195).[13,14] The resulting ICURs for dulaglutide compared with liraglutide 1.8 mg and/or GLP-1 analogues as a class in the second- and third-line settings were not affected. For all other comparators, the ICURs increased compared with the manufacturer's base-case analysis.
- **Removal of BMI as a driver of clinical complications in third-line analysis:** To avoid double-counting of benefits related to BMI reduction, the effect of this parameter on the risk of diabetes-related complication was set to 0 for the analysis comparing dulaglutide with insulin glargine based on the AWARD-2 trial (it was already set to 0 for all other third-line analyses in the manufacturer's base-case analyses). This resulted in a slight increase in ICURs for dulaglutide versus insulin glargine.
- **Disutility associated with SMBG:** The manufacturer's second- and third-line analyses applied a disutility value for each SMBG test, based on an unspecified source. The appropriateness of this disutility was uncertain due to the lack of information on how it was derived and its validity, and the limited evidence on disutility associated with SMBG in the literature. The manufacturer provided one-way sensitivity analyses abolishing the disutility with SMBG. The resulting ICURs for dulaglutide compared with liraglutide 1.8 mg or GLP-1 analogues as a class were not affected. For all other comparators, the ICURs increased compared with the manufacturer's base-case analysis.

- **Comparators as add-on to metformin and metformin plus a sulfonylurea:** Using efficacy data from the manufacturer-submitted NMAs for second- and third-line therapies, CDR conducted scenario analyses that compared dulaglutide 0.75 mg and 1.5 mg to DPP-4 inhibitors (linagliptin, $2.25/day, Nova Scotia drug benefit list, 2016)[8] and SGLT2 inhibitors (dapagliflozin, $2.45/day, Quebec drug benefit list)[7] in the second- and third-line therapy settings. Compared with DPP-4 inhibitors at second-line, ICURs were in excess of $400,000 per QALY based on the manufacturer's base-case inputs, and compared with SGLT2 inhibitors, ICURs were above $2 million per QALY. At third-line, the ICURs for dulaglutide versus DPP-4 inhibitors were above $300,000 per QALY; dulaglutide 0.75 mg was dominated by SGLT2 inhibitors, while the ICUR for dulaglutide 1.5 mg versus SGLT2 inhibitors was more than $800,000 per QALY.
- **Cost of basal insulin:** To examine the effect of including insulin NPH as a comparator, CDR conducted reanalyses for both the second-line and third-line settings that assumed similar efficacy between insulin NPH and insulin glargine, at a cost per 10 mL vial (Novolin ge NPH 100 U/mL) of $22.56 (Ontario Drug Benefit, 2016).[9] As expected, the ICURs were higher in this analysis compared with the base-case analysis: more than $207,000 and $170,000 per QALY for dulaglutide 0.75 mg and 1.5 mg, respectively, versus insulin NPH in the second-line setting; and more than $96,000 and $80,000 per QALY, respectively, in the third-line setting (based on AWARD-2 data; similar results in analysis based on data from NMA).

CDR's base-case analysis simultaneously incorporated revised baseline prevalence of complications to align with the CADTH OU reports (for second-line analyses), revised price of liraglutide, the disutility of weight gain from the CADTH OU reports, and removal of the disutility associated with SMBG. As well, the effect of BMI on long-term complications was set to 0 to avoid double-counting in the CDR base-case analysis of third-line therapy comparing dulaglutide with insulin glargine based on the AWARD-2 trial.

Price Reduction Scenarios

A price reduction analysis was conducted on both the manufacturer's base-case analysis and the CDR base-case analysis. For both the manufacturer's and CDR's base-case analyses, the results showed that a price reduction of between 10% and 75% would reduce the ICURs of dulaglutide to below $50,000 per QALY, depending upon the choice of comparator and therapy setting. Full results of the price reduction analyses for dulaglutide for both the manufacturer and CDR base-case analyses of the second- and third-line settings are presented in Table 5 and Table 6, respectively.

TABLE 3: SUMMARY OF RESULTS OF CADTH COMMON DRUG REVIEW REANALYSES FOR SECOND-LINE THERAPY

	ICUR ($/QALY)	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg
Dulaglutide 1.5 mg vs. liraglutide 1.8 mg as add-on to metformin based on AWARD-6		
Manufacturer's base case	NA	Dulaglutide dominant[a]
Revised baseline clinical characteristics[b]	NA	Dulaglutide dominant[a]
Cost of liraglutide from Quebec drug benefit list ($6.49/day)	NA	402,445
Alternate disutility for weight gain (–0.00195)	NA	Dulaglutide dominant[a]
No disutility with SMBG testing	NA	Dulaglutide dominant[a]
CDR base case[c]	**NA**	**174,981**
Dulaglutide vs. GLP-1 analogue class as add-on to metformin based on NMA		
Manufacturer's base case	Dulaglutide less costly, less effective	Dulaglutide less costly, less effective
Revised baseline clinical characteristics[b]	GLP-1 dominant[a]	GLP-1 dominant[a]
Cost of liraglutide from Quebec drug benefit list ($6.49/day)	GLP-1 dominant[a]	GLP-1 dominant[a]
Alternate disutility for weight gain (–0.00195)	GLP-1 dominant[a]	GLP-1 dominant[a]
No disutility with SMBG testing	GLP-1 dominant[a]	GLP-1 dominant[a]
CDR base case[c]	**GLP-1 dominant[a]**	**GLP-1 dominant[a]**
Dulaglutide vs. sulfonylurea as add-on to metformin		
Manufacturer's base case	185,013	165,971
Revised baseline clinical characteristics[b]	185,224	166,014
Alternate disutility for weight gain (–0.00195)	225,703	203,947
No disutility with SMBG testing	219,355	192,468
CDR base case[d]	**278,510**	**245,380**
Dulaglutide vs. basal insulin as add-on to metformin		
Manufacturer's base case	126,049	104,402
Revised baseline clinical characteristics[b]	124,925	103,628
Cost of Novolin ge NPH insulin from Ontario Drug Benefit list ($2.26/mL)	207,206	170,356
Alternate disutility for weight gain (–0.00195)	151,700	125,892
No disutility with SMBG testing	297,053	195,497
CDR base case[d]	**511,896**	**293,380**
Dulaglutide vs. biphasic insulin as add-on to metformin		
Manufacturer's base case	9,101	9,356
Revised baseline clinical characteristics[b]	9,046	9,287
Alternate disutility for weight gain (–0.00195)	10,178	10,509
No disutility with SMBG testing	11,342	11,426
CDR base case[d]	**13,180**	**13,334**
Dulaglutide vs. DPP-4 as add-on to metformin		
Base case using cost of linagliptin from Nova Scotia drug benefit list ($2.25/day)	740,999	436,990
Alternate disutility for weight gain (–0.00195)	1,478,625	714,133
No disutility with SMBG testing	740,999[e]	436,990[e]

	ICUR ($/QALY)	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg
CDR base case[f]	**1,478,625**	**714,133**
Dulaglutide vs. SGLT2 as add-on to metformin		
Base case using cost of dapagliflozin from Quebec drug benefit list ($2.45/day)	3,172,351	760,694
Alternate disutility for weight gain (-0.00195)	2,577,279	870,993
No disutility with SMBG testing	3,172,351[e]	760,694[e]
CDR base case[f]	**2,577,279**	**870,993**

CDR = CADTH Common Drug Review; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; NA = not applicable; QALY = quality-adjusted life-year; SGLT2 = sodium/glucose cotransporter 2; SMBG = self-monitoring blood glucose; vs. = versus.

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

[b] The baseline clinical characteristics in the manufacturer-submitted technical model for the second-line analyses (comparing dulaglutide with GLP-1 analogues, sulfonylurea, and basal and biphasic insulins) did not correspond to the values specified in the manufacturer-submitted report for dulaglutide as second-line treatment: baseline characteristics based on AWARD-2 (i.e., third-line setting) were used by the manufacturer instead of values from the CADTH Optimal Use (OU) report for second-line treatments. These were revised to reflect the CADTH second-line therapy OU report.

[c] Multi-way r-analysis using revised cost for liraglutide, cohort, alternate disutility for weight gain (–0.00195), and no SMBG disutility.

[d] Multi-way reanalysis using corrected cohort, alternate disutility for weight gain (–0.00195), and no SMBG disutility.

[e] Manufacturer's model assumes that DPP-4 and SGLT2 inhibitors have the same testing frequency as GLP-1 analogues (3.86 tests per week); eliminating the disutility with SMBG has no impact on results.

[f] Multi-way reanalysis using alternate disutility for weight gain (–0.00195) and no SMBG disutility.

TABLE 4: SUMMARY OF RESULTS OF CADTH COMMON DRUG REVIEW REANALYSES FOR THIRD-LINE THERAPY

	ICUR ($/QALY)	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg
Dulaglutide vs. insulin glargine as add-on to metformin + a sulfonylurea based on AWARD-2		
Manufacturer's base case	66,674	56,016
Excluding BMI as a driver of clinical complications	72,565	62,001
Cost of Novolin ge NPH insulin from Ontario Drug Benefit list ($2.26/mL)	96,327	80,871
Alternate disutility for weight gain (–0.00195)	101,975	88,736
No disutility with SMBG testing	105,510	82,444
CDR base case[a]	**181,705**	**137,552**
Dulaglutide vs. GLP-1 analogue class as add-on to metformin + a sulfonylurea based on NMA		
Manufacturer's base case	Dulaglutide dominant[b]	Dulaglutide dominant[b]
Cost of liraglutide from Quebec drug benefit list ($6.49/day)	70,744	52,047
Alternate disutility for weight gain (–0.00195)	Dulaglutide dominant[b]	Dulaglutide dominant[b]
No disutility with SMBG testing	Dulaglutide dominant[b]	Dulaglutide dominant[b]
CDR base case[c]	**51,655**	**46,608**
Dulaglutide vs. basal insulin as add-on to metformin + a sulfonylurea based on NMA		
Manufacturer's base case	62,152	56,057
Cost of Novolin ge NPH insulin from Ontario drug benefit list ($2.26/mL)	99,040	87,339
Alternate disutility for weight gain (-0.00195)	83,723	76,001
No disutility with SMBG testing	93,386	78,252

	ICUR ($/QALY)	
	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg
CDR base case[d]	**152,378**	**123,487**
CDR base case using cost of Novolin ge NPH as basal insulin[d]	**242,816**	**192,397**
Dulaglutide vs. biphasic insulin as add-on to metformin + a sulfonylurea based on NMA		
Manufacturer's base case	10,820	11,740
Alternate disutility for weight gain (–0.00195)	18,270	19,858
No disutility with SMBG testing	17,627	18,353
CDR base case[d]	**29,163**	**29,506**
Dulaglutide vs. DPP-4 inhibitors as add-on to metformin + a sulfonylurea based on NMA		
Base case using cost of linagliptin from Nova Scotia drug benefit list ($2.25/day)	341,319	217,739
Alternate disutility for weight gain (–0.00195)	467,936	304,491
No disutility with SMBG testing	341,319[e]	217,739[e]
CDR base case[d]	**467,936**	**304,491**
Dulaglutide vs. SGLT2 as add-on to metformin + a sulfonylurea based on NMA		
Base case using cost of dapagliflozin from Quebec drug benefit list ($2.45/day)	SGLT2 dominant[b]	1,029,731
Alternate disutility for weight gain (–0.00195)	846,266	422,943
No disutility with SMBG testing	SGLT2 dominant[b,e]	1,029,731[e]
CDR base case[d]	**846,266**	**422,943**

BMI = body mass index; 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; SGLT2 = sodium/glucose cotransporter 2; SMBG = self-monitoring of blood glucose; vs. = versus.

[a] Multi-way reanalysis excluding BMI as driver of clinical complications, revised disutility for weight gain (–0.00195), and no SMBG disutility.

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

[c] Multi-way reanalysis using revised cost for liraglutide, revised disutility for weight gain (–0.00195), and no SMBG disutility.

[d] Multi-way reanalysis using revised disutility for weight gain (–0.00195) and no SMBG disutility.

[e] Manufacturer's model assumes that DPP-4 and SGLT2 inhibitors have the same testing frequency as GLP-1 analogues (3.86 tests per week); eliminating the disutility with SMBG has no impact on results.

TABLE 5: CADTH COMMON DRUG REVIEW PRICE REDUCTION SCENARIOS FOR DULAGLUTIDE IN SECOND-LINE THERAPY

			ICURs for Dulaglutide Versus Comparators ($/QALY)	
Comparator		Dulaglutide price reduction	Manufacturer's base case	CDR base case[a]
Dulaglutide 0.75 mg	Basal insulin	Submitted	126,049	511,896
		25% lower	49,873	202,596
		30% lower	34,637	140,736
		35% lower	19,401	78,876
		40% lower	4,166	17,016
		50% lower	Dulaglutide dominant[b]	Dulaglutide dominant[b]
	GLP-1 analogues (based on NMA)	Submitted	Dulaglutide less costly and less effective	GLP-1 analogues dominant[b]
		15% lower	Dulaglutide less costly and less effective	Dulaglutide less costly and less effective
	Sulfonylureas	Submitted	185,013	278,510
		50% lower	85,068	125,706
		75% lower	32,513	49,304
	DPP-4 inhibitors	Submitted	740,999	1,478,625
		50% lower	179,104	357,393
		60 % lower	66,725	133,147
		65 % lower	10,536	21,023
		75% lower	Dulaglutide dominant[b]	Dulaglutide dominant[b]
	SGLT2 inhibitors	Submitted	3,172,351	2,577,279
		50 % lower	664,515	539,865
		60% lower	162,948	132,382
		65% lower	Dulaglutide dominant[b]	Dulaglutide dominant[b]
Dulaglutide 1.5 mg	Liraglutide 1.8 mg (based on AWARD-6)	Submitted	Dulaglutide dominant[b]	174,981
		25% lower	Dulaglutide dominant[b]	Dulaglutide dominant[b]
	Basal insulin	Submitted	104,402	293,380
		25% lower	40,747	114,526
		30% lower	28,016	78,755
		35% lower	15,285	42,984
		40% lower	2,554	7,214
		50 % lower	Dulaglutide dominant[b]	Dulaglutide dominant[b]
	GLP-1 analogues (NMA)	Submitted	Dulaglutide less costly and less effective	GLP-1 analogues dominant[b]
		15% lower	Dulaglutide less costly and less effective	Dulaglutide less costly and less effective
	Sulfonylurea	Submitted	165,971	245,380
		50% lower	73,228	108,451
		60% lower	54,845	81,065
		75% lower	26,856	39,986
	DPP-4 inhibitors	Submitted	436,990	714,133
		50% lower	101,817	166,390

Comparator		Dulaglutide price reduction	ICURs for Dulaglutide Versus Comparators ($/QALY)	
			Manufacturer's base case	CDR base case[a]
		60% lower	34,372	56,842
		75% lower	Dulaglutide dominant[b]	Dulaglutide dominant[b]
	SGLT2 inhibitors	Submitted	760,694	870,993
		50 % lower	152,950	175,127
		60 % lower	31,401	35,954
		75% lower	Dulaglutide dominant[b]	Dulaglutide dominant[b]

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SGLT2 = sodium/glucose cotransporter 2; SMBG = self-monitoring of blood glucose.

[a] Includes revised patient baseline clinical characteristics to align with CADTH second-line Optimal Use (OU) report, use of alternate disutility with weight gain (–0.00195) elimination of disutility with SMBG, and revised price for liraglutide (for comparisons with liraglutide or GLP-1 analogues).

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

TABLE 6: CADTH COMMON DRUG REVIEW PRICE REDUCTION SCENARIOS FOR DULAGLUTIDE IN THIRD-LINE THERAPY

			ICURs for Dulaglutide Versus Comparators ($/QALY)	
Comparator		Dulaglutide Price Reduction	Manufacturer's Base Case	CDR Base Case[a]
Dulaglutide 0.75 mg	Insulin glargine (based on AWARD-2)	Submitted	66,674	181,705
		25% lower	38,351	96,482
		50% lower	2,692	11,259
	Basal insulin (based on NMA)	Submitted	62,152	152,378
		10% lower	41,988	115,583
		25% lower	24,632	60,390
		50% lower	Dulaglutide dominant[b]	Dulaglutide dominant[b]
	GLP-1 analogues	Submitted	Dulaglutide dominant[b]	51,655
		10% lower	Dulaglutide dominant[b]	13,542
	DPP-4 inhibitors	Submitted	341,319	467,936
		25% lower	199,649	273,711
		50% lower	57,979	79,487
		60% lower	1,311	1,797
	SGLT2 inhibitors	Submitted	SGLT2 inhibitors dominant[b]	846,266
		50% lower	SGLT2 inhibitors dominant[b]	145,512
		60% lower	SGLT2 inhibitors dominant[b]	5,361
		75% lower	Dulaglutide less costly and less effective	Dulaglutide dominant[b]
Dulaglutide 1.5 mg	Insulin glargine (based on AWARD-2)	Submitted	56,056	137,552
		25% lower	28,191	70,741
		50% lower	Dulaglutide dominant[b]	3,930
	Basal insulin (based on NMA)	Submitted	56,057	123,487
		10% lower	37,505	93,568
		25% lower	22,103	48,689
	GLP-1 analogues	Submitted	Dulaglutide dominant[b]	46,608
		10% lower	Dulaglutide dominant[b]	15,879
	DPP-4 inhibitors	Submitted	217,739	304,491
		25% lower	125,332	175,267
		50% lower	32,926	46,044
	SGLT2 inhibitors	Submitted	1,029,731	422,943
		25% lower	591,682	243,022
		50% lower	153,632	63,102
		60% lower	Dulaglutide dominant[b]	Dulaglutide dominant[b]

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; SGLT2 = sodium/glucose cotransporter 2; SMBG = self-monitoring of blood glucose.

[a] Includes alternate disutility with weight gain (–0.00195) and elimination of disutility with SMBG.

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

6. ISSUES FOR CONSIDERATION

The manufacturer's base-case analyses comparing dulaglutide to basal insulin were based on the efficacy and price of insulin glargine (Lantus) at the price of $61.69 for a 10 mL vial of 100 U/mL (Ontario Drug Benefit, February 2016).[9] A subsequent entry biologic (SEB) of insulin glargine, Basaglar, was approved by Health Canada in September 2015[25] and is available at a price 15% lower than that of the list price for the reference product (Lantus).[10] Basaglar is under review by CDR, and is currently not reimbursed by CDR-participating drug plans. Using the price of Basaglar in the analyses is expected to increase the ICURs of dulaglutide compared with insulin glargine in both the second- and third-line settings.

7. PATIENT INPUT

According to patient group input received by CDR, once-weekly administration was seen as an advantage of dulaglutide. Patient input also described weight loss to be an important consideration in the choice of treatment, although there were no direct comments regarding the effects of weight gain or loss associated with diabetes treatments on perceived health status or quality of life. Patients noted the adverse events associated with dulaglutide, such as increased gastrointestinal effects, dehydration, and urinary tract or yeast infections. Overall, the manufacturer's economic submission captured outcomes of importance to patients such as changes in A1C and weight, and their impact on costs and quality of life. However, adverse effects other than hypoglycemia were not captured.

8. CONCLUSIONS

According to CDR's base-case analyses for second- and third-line therapy, dulaglutide was likely to be cost-effective only at conventional thresholds compared with biphasic insulin. Dulaglutide was unlikely to be cost-effective compared with basal insulin (insulin glargine) for either second-line therapy in combination with metformin, or third-line therapy in combination with metformin plus a sulfonylurea. Price reductions of 25% or more would be required, according to the CDR base case, for dulaglutide to be considered cost-effective versus insulin glargine, with larger reductions required in comparison with insulin NPH and SEB insulin glargine.

For second-line therapy compared with sulfonylureas, and for second- and third-line therapy compared with DPP-4 inhibitors or SGLT2 inhibitors, dulaglutide was associated with high ICURs (> $200,000/QALY) in CDR's base-case analyses. Price reductions of dulaglutide of 50% or more would be required for ICURs to fall in a range that may be considered cost-effective in comparison with these drugs.

A cost-minimization analysis was considered sufficient for the comparison of dulaglutide with other GLP-1 analogues, as the manufacturer's indirect comparison reported no significant differences in efficacy or safety. At the submitted price, dulaglutide is more costly than liraglutide (based on the mean dose referenced by the manufacturer) and daily exenatide (price reductions of 5.5% and 71.6%, respectively, are required for price parity), and the same cost as weekly exenatide.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 7 have been deemed to be appropriate by the clinical expert consulted by the CADTH Common Drug Review (CDR). Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such, it may not represent the actual costs to public drug plans.

TABLE 7: COST COMPARISON TABLE FOR NON-INSULIN ANTIDIABETIC DRUGS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
GLP-1 receptor analogue						
Dulaglutide (Trulicity)	**0.75 mg/0.5 mL 1.5 mg/0.5 mL**	**4 x 0.5 mL pre-filled pen**	**191.8000[a]**	**0.75 mg to 1.5 mg once weekly**	**6.85**	**2,493**
Exenatide (Bydureon)	2 mg	2 mg pre-filled pen	47.9400[b]	2 mg once weekly	6.85	2,493
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/mL)	119.7250[b]	5 to 10 mcg twice daily	3.99	1,457
Liraglutide (Victoza)	2 x 3 mL 3 x 3 mL	Pre-filled pen (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
Biguanides						
Metformin	500 mg 850 mg	tab	0.0444 0.0610[d]	500 mg 3 to 4 times daily	0.18 to 0.23	49 to 65
Sulfonylureas						
Gliclazide (generics)	80 mg	tab	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 tab	0.0931 0.2150	30 mg to 120 mg daily	0.09 to 0.43	34 to 157
Glimepiride (generics)	1 mg 2 mg 4 mg	tab	0.3857[c]	1 mg to 4 mg daily	0.39	142
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
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	2.5500	5 mg daily	2.55	931

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
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 mg/500 mg 12.5 mg/850 mg 12.5 mg/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
SGLT2 inhibitors						
Canagliflozin (Invokana)	100 mg 300 mg	tab	2.6960	100 or 300 mg daily	2.70	986
Dapagliflozin (Forxiga)	5 mg 10 mg	tab	2.4500[c]	5 or 10 mg daily	2.45	894
Empagliflozin (Jardiance)	10 mg 25 mg	tab	2.6200[e]	10 or 25 mg daily	2.62	956
Thiazolidinediones						
Pioglitazone (generics)	15 mg 30 mg 45 mg	tab	0.3800[f] 0.5360[f] 0.8075[f]	15 mg to 45 mg daily	0.38 to 0.81	139 to 295
Rosiglitazone (Avandia)	2 mg 4 mg 8 mg	tab	1.3755[f] 2.1584[f] 3.0865[f]	4 to 8 mg daily	2.16 to 3.09	788 to 1,126
Rosiglitazone/ metformin (Avandamet)	2/500 mg 4/500 mg 2/1,000 mg 4/1,000 mg	tab	1.1611[f] 1.5946[f] 1.2682[f] 1.7337[f]	4/1,000 to 8/2,000 mg daily in divided doses	2.32 to 3.47	847 to 1,266

DPP-4 = dipeptidyl peptidase-4; ER = extended release; GLP-1 = glucagon-like peptide-1; SLGT2 = sodium/glucose cotransporter 2; tab = tablet.

[a] Manufacturer's submission price.[3,4]

[b] IMS Delta PA. IMS Brogan (March 2016).[10]

[c] Régie de l'assurance maladie du Québec (RAMQ) (February 2016).[7]

[d] Alberta Drug Formulary (February 2016).[26]

[e] CADTH Canadian Drug Expert Committee Final Recommendation for Empagliflozin (Jardiance: Boehringer Ingelheim [Canada] Ltd.), October 15, 2015.[27]

[f] Saskatchewan Drug Formulary (February 2016).[28]

Source: Ontario Drug Benefit (February 2016) prices unless otherwise indicated.[9]

TABLE 8: COST COMPARISON OF INSULIN DRUGS

Drug/Comparator	Strength	Dosage Form	Price ($)	Cost per mL ($)
Short-acting insulins				
Insulin aspart (NovoRapid)	100 U/mL	5 x 3mL cartridge 5 x 3mL disposable pen 10 mL vial	58.81 61.21 29.00	3.92 4.08 2.90
Insulin glulisine (Apidra)	100 U/mL	5 x 3 mL cartridge 5 x 3 disposable pen 10 mL vial	50.00 50.35 25.23	3.33 3.36 2.52
Insulin lispro (Humalog)	100 U/mL	5 x 3 mL cartridge 5 x 3 mL disposable pen 10m L vial	56.38 55.27 28.02	3.76 3.68 2.80
Regular human insulin (Humulin R)	100 U/mL	5 x 3 mL cartridge 10 mL vial	45.12 22.99	3.01 2.30
Regular human insulin (Novolin ge Toronto)	100 U/mL	5 x 3 mL cartridge 10 mL vial	43.30 22.06	2.89 2.21
Insulin NPH				
Humulin N	100 U/mL	5 x 3 mL cartridge 10 mL vial	45.12 22.99	3.01 2.30
Novolin ge NPH	100U/mL	5 x 3 mL cartridge 10 mL vial	44.34 22.56	2.96 2.26
Long-acting insulin analogues				
Insulin glargine (Lantus)	100 U/mL	5 x 3 mL cartridge 5 x 3 disposable pen 10 mL vial	92.85 92.85 61.69	6.19 6.19 6.17
Insulin glargine (Basaglar)	100 U/mL	5 x 3mL cartridge 5 x 3 pre-filled pen	78.92[a] 78.92[a]	5.26 5.26
Insulin detemir (Levemir)	100 U/mL	5 x 3 mL cartridge 5 x 3 mL disposable pen	106.76 107.29	7.12 7.15
Pre-mixed insulins				
Biphasic insulin aspart 30/70 (NovoMix 30)	100 U/mL	5 x 3 mL cartridge	55.37	3.69
Lispro/lispro protamine 25/75 (Humalog Mix 25)	100 U/mL	5 x 3 mL cartridge 5 x 3 mL disposable pen	56.65 55.92	3.78 3.73
Lispro/lispro protamine 50/50 (Humalog Mix 50)	100 U/mL	5 x 3 mL cartridge 5x3mL disposable pen	55.48 54.99	3.70 3.67
Humulin 30/70	100 U/mL	5 x 3 mL cartridge 10 mL vial	45.12 22.99	3.01 2.30
Novolin ge 30/70	100 U/mL	5 x 3 mL cartridge 10 mL vial	43.82 22.68	2.92 2.27
Novolin ge 40/60	100 U/mL	5 x 3 mL cartridge	44.14	2.94
Novolin ge 50/50	100U/mL	5 x 3 mL cartridge	44.14	2.94

[a] IMS Delta PA. IMS Brogan (March 2016).[10]
Source: Ontario Drug Benefit (February 2016) prices.[9]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DULAGLUTIDE RELATIVE TO GLICLAZIDE AS ADD-ON TO METFORMIN BASED ON NETWORK META-ANALYSIS?

Dulaglutide vs. Gliclazide	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[a]	Dulaglutide 0.75 mg: $185,013 per QALY Dulaglutide 1.5 mg: $165,971 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
[a] Based on manufacturer's results[3]

TABLE 10: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DULAGLUTIDE RELATIVE TO LIRAGLUTIDE AS ADD-ON TO METFORMIN BASED ON THE AWARD-6 TRIAL?

Dulaglutide Vs. Liraglutide	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[a]	Dulaglutide 1.5 mg dominated liraglutide					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
[a] Based on manufacturer's results.[3]

TABLE 11: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DULAGLUTIDE RELATIVE TO LIRAGLUTIDE AS ADD-ON TO METFORMIN BASED ON NETWORK META-ANALYSIS RESULTS?

Dulaglutide Vs. Liraglutide	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[a]	Dulaglutide less costly and less effective than liraglutide					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
[a] Based on manufacturer's results.[3]

TABLE 12: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DULAGLUTIDE RELATIVE TO INSULIN GLARGINE AS ADD-ON TO METFORMIN BASED ON NETWORK META-ANALYSIS RESULTS?

Dulaglutide Vs. Insulin Glargine	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[a]	Dulaglutide 0.75 mg: $126,049 per QALY Dulaglutide 1.5 mg: $104,402 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
[a] Based on manufacturer's results.[3]

TABLE 13: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DULAGLUTIDE RELATIVE TO BIPHASIC INSULIN AS ADD-ON TO METFORMIN BASED ON NETWORK META-ANALYSIS RESULTS?

Dulaglutide Vs. Biphasic Insulin	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[a]	Dulaglutide 0.75 mg: $9,101 per QALY Dulaglutide 1.5 mg: $9,356 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
[a] Based on manufacturer's results.[3]

TABLE 14: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DULAGLUTIDE RELATIVE TO INSULIN GLARGINE AS ADD-ON TO METFORMIN PLUS A SULFONYLUREA BASED ON THE AWARD-2 TRIAL?

Dulaglutide Vs. Insulin Glargine	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[a]	Dulaglutide 0.75 mg: $66,674 per QALY Dulaglutide 1.5 mg: $56,016 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
[a] Based on manufacturer's results.[4]

TABLE 15: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DULAGLUTIDE RELATIVE TO BASAL INSULIN (REPRESENTED BY INSULIN GLARGINE) AS ADD-ON TO METFORMIN PLUS A SULFONYLUREA BASED ON NETWORK META-ANALYSIS RESULTS?

Dulaglutide Vs. Insulin Glargine	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[a]	Dulaglutide 0.75 mg: $62,152 per QALY Dulaglutide 1.5 mg: $56,057 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
[a] Based on manufacturer's results.[4]

TABLE 16: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DULAGLUTIDE RELATIVE TO BIPHASIC INSULIN AS ADD-ON TO METFORMIN PLUS A SULFONYLUREA BASED ON NETWORK META-ANALYSIS RESULTS?

Dulaglutide Vs. Biphasic Insulin	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[a]	Dulaglutide 0.75 mg: $10,820 per QALY Dulaglutide 1.5 mg: $11,740 per QALY					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year.
[a] Based on manufacturer's results.[4]

TABLE 17: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS DULAGLUTIDE RELATIVE TO GLP-1 ANALOGUES (REPRESENTED BY LIRAGLUTIDE) AS ADD-ON TO METFORMIN PLUS A SULFONYLUREA BASED ON NETWORK META-ANALYSIS RESULTS?

Dulaglutide Vs. Liraglutide	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*	Liraglutide dominated by dulaglutide					

CE = cost-effectiveness; GLP-1 = glucagon-like peptide-1; NA = not applicable; QALY = quality-adjusted life-year.
[a] Based on manufacturer's results.[4]

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 18: 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 19: AUTHORS' INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to the 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 DULAGLUTIDE

TABLE 20: FINDINGS OF OTHER HEALTH TECHNOLOGY ASSESSMENT ORGANIZATIONS

	Scottish Medicines Consortium (January 2016)[29]
Treatment	• Dulaglutide 1.5 mg once weekly as third-line treatment
Price	• £18.31/week
Similarities with CDR submission	• Use of trials from the AWARD program (AWARD-1 and -2) • Use of a CUA considering a lifetime horizon • Consideration of use as a third-line drug
Differences with CDR submission	• Considered both a CMA and a CUA • Did not consider use as a second-line drug • Only considered the economic case for the 1.5 mg dosage form • Only considered other GLP-1 analogues as comparators • CUA used the IMS CORE model rather than UKPDS equations
Manufacturer's results	• CMA: considering only drug and needle costs, dulaglutide is cost-saving compared with liraglutide (1.2 mg, 1.8 mg, and average daily dose) and exenatide ER. • CUA: dulaglutide is dominant when compared with lixisenatide and exenatide twice daily.
Issues noted by the review group	• The CMA made use of an ITC. While the ITC found that there were differences in rates of adverse events among the GLP-1 analogues, the assumption of no differences was made for the sake of simplicity and to allow the use of a CMA approach. • In the CUA, only the comparison with exenatide was based on direct evidence; all other comparisons were based on an ITC.
Results of reanalyses by the review group (if any)	• No reanalyses were presented; SMC considered the economic case made by the manufacturer to be sound.
Recommendation	• Accepted for restricted use within NHS Scotland.

CDR = CADTH Common Drug Review; CMA = cost-minimization analysis; CUA = cost-utility analysis; ER = extended release; GLP-1 = glucagon-like peptide-1; ITC = indirect treatment comparison; NHS = National Health Service; SMC = Scottish Medicines Consortium; UKPDS = United Kingdom Prospective Diabetes Study.

APPENDIX 5: REVIEWER WORKSHEETS

Additional Information Regarding Manufacturer's Model

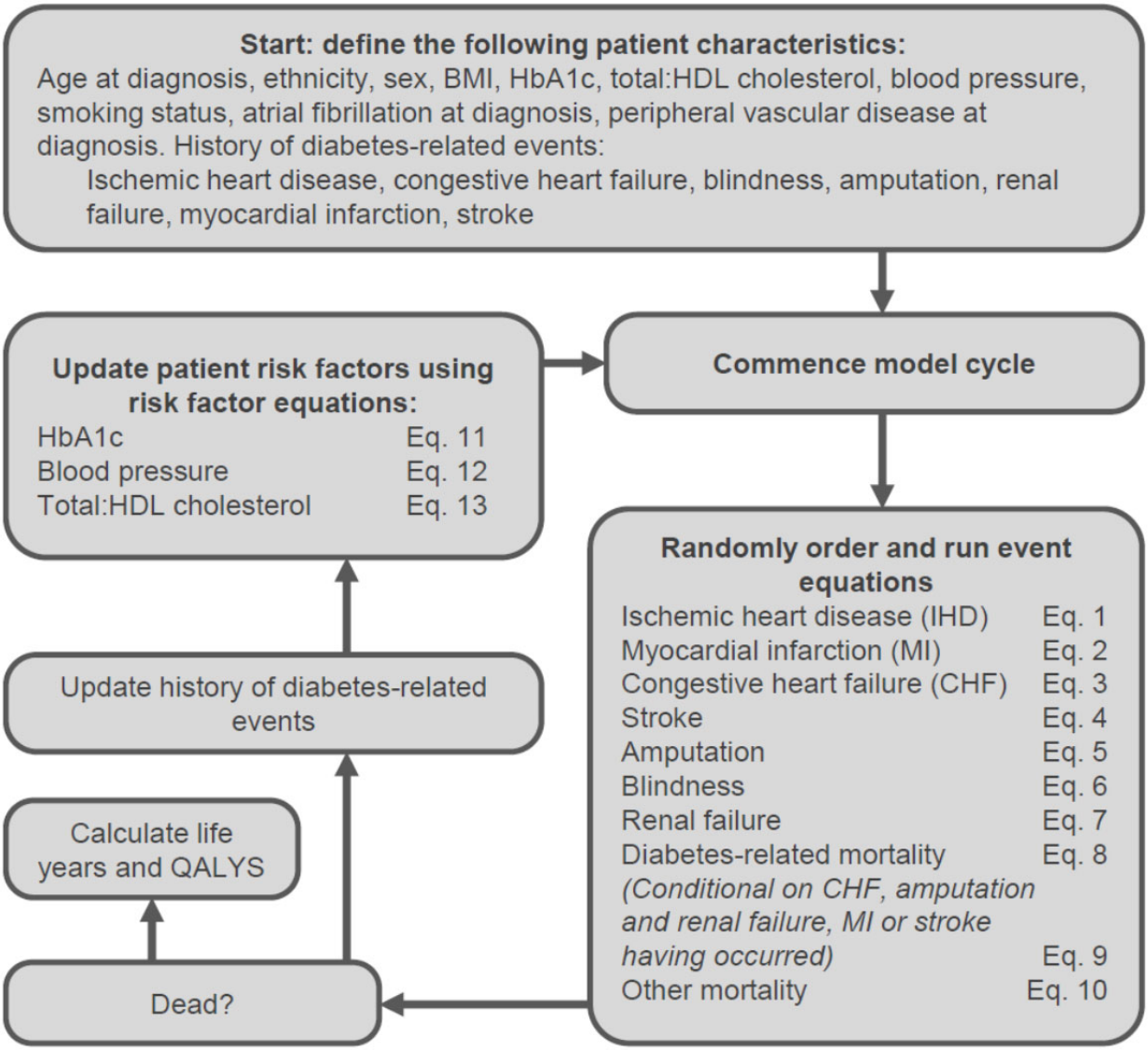
The cost-utility analyses (CUAs) were conducted using the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model, a discrete event simulation model based on data from the UKPDS that predict longer-term diabetes-related complications based on patient characteristics and management of glycated hemoglobin (A1C). The UKPDS was a large-scale randomized clinical trial that evaluated policies for intensive blood glucose and blood pressure control.[11] Between 1977 and 1991, 5,102 patients with newly diagnosed type 2 diabetes, aged 25 to 65 years, who were subsequently shown to have a fasting plasma glucose greater than 6 mmol/L on two occasions and who had no recent history of myocardial infarction (MI), ischemic heart disease, congestive heart failure, more than one major vascular event, or a severe concurrent illness that would limit life expectancy were recruited to the study.

The UKPDS Outcomes Model was based on data from 39,460 person-years of follow-up from 3,642 patients (white, Asian-Indian, and Afro-Caribbean) in the UKPDS for whom annual data on potential risk factors were available. The original model was described as a "probabilistic discrete-time illness–death model" with the aim of estimating the first occurrence of each of seven diabetes-related complications (fatal or non-fatal MI, other ischemic heart disease, stroke, heart failure, amputation, renal failure, and eye disease measured in terms of blindness in one eye) and death in order to estimate lifetime outcomes and quality-adjusted life expectancy. Risk equations in the UKPDS Outcomes Model were based on data from patients with a median follow-up of 10.3 years. The model developed for the present analysis is based exclusively on the UKPDS Outcomes Model as described by Clarke and colleagues (2004).[30]

The manufacturer included the following modifications to the existing UKPDS Outcomes Model:

- Association of each treatment with non-severe and severe hypoglycemia rates and disutility values
- Incorporation of a disutility with each unit increase in body mass index (BMI) above a defined threshold, and enabling the specification of the duration of the disutility effect. The model also incorporated an option to remove BMI as a risk factor for diabetes-related complications in the UKPDS equations to avoid double-counting when a BMI-related disutility is specified in the model
- A treatment intensification threshold can be configured based on either an A1C threshold or a time point
- Additional treatment effects and costs associated with a user-defined treatment can be applied
- Differences between treatments in UKPDS risk factors (A1C, systolic blood pressure [SBP], and total cholesterol to high-density lipoprotein [HDL] ratio), BMI, costs, and hypoglycemia rates can be abolished
- Ability to associate a disutility and effect duration with each self-monitoring of blood glucose (SMBG) test.[30]

FIGURE 1: UNITED KINGDOM PROSPECTIVE DIABETES STUDY MODEL STRUCTURE



BMI = body mass index; CHF = congestive heart failure; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; MI = myocardial infarction; QALY = quality-adjusted life-year.
Source: Pharmacoeconomic submissions; Figure 7, page 25.[3]

TABLE 21: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Analyses as second-line treatment: • Analysis of dulaglutide 1.5 mg compared with liraglutide 1.8 mg was based on the AWARD-6 trial, an open-label, active-controlled phase 3 non-inferiority trial that enrolled participants with T2DM from nine countries, none of which were from Canada.[5,12] Participants were randomized (1:1) to receive subcutaneously injected once-weekly dulaglutide 1.5 mg or subcutaneously injected once-daily liraglutide 1.8 mg. The AWARD-6 trial comprised a screening period of two weeks, a treatment period of 26 weeks, and a safety follow-up of four weeks.[5,12] • Analyses of dulaglutide 0.75 mg and 1.5 mg compared with sulfonylureas, GLP-1 analogues, and basal and biphasic insulin were based on a manufacturer-submitted NMA of second-line therapies that included 51 trials (including AWARD-6) and contained 27 different treatments including DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, and alpha-glucosidase inhibitors in addition to dulaglutide, sulfonylurea, GLP-1 analogues, and insulin regimens.[2] Analyses as third-line treatment: • Analysis of dulaglutide 0.75 mg and 1.5 mg compared with insulin glargine was based on the AWARD-2 trial, an open-label, active-controlled, phase 3 non-inferiority trial that enrolled participants with T2DM from 20 countries, including Canada.[6,12] Participants were randomized (1:1:1) to receive subcutaneously injected once-weekly dulaglutide 0.75 mg, dulaglutide 1.5 mg, or once-daily insulin glargine. The AWARD-2 trial comprised a lead-in period of 10 weeks, a treatment period of 78 weeks, and a safety follow-period of four weeks.[6,12] • Analyses of dulaglutide 0.75 mg and 1.5 mg compared with biphasic insulin and GLP-1 analogues were based on a manufacturer-submitted NMA of third-line therapies that included 29 trials (including AWARD-2) and contained 13 treatments including DPP-4 inhibitors, SGLT2 inhibitors, and thiazolidinediones in addition to dulaglutide and insulin regimens.[2]	Dulaglutide 0.75 mg was not studied in the AWARD-6 trial.
Patient characteristics	For second-line: • Analysis populations were based on data from an NMA of second-line therapies supplemented with data from the AWARD-6 trial.[5,12]	Based on the data sources used by the manufacturer, the proportion of patients with myocardial infarctions in second-

Data Input	Description of Data Source	Comment
	• Proportion of patients with a history of diabetes-related complications at baseline was taken from the CADTH 2010 Third-Line Therapy report.[31] For third-line: • Analysis population was based on data from the AWARD-2 trial.[6,12] • Proportion of patients with a history of diabetes-related complications at baseline was taken from the AWARD-2 trial and the CADTH 2010 Third-Line Therapy report.[6,12,31]	line are higher than in third-line, which may not be clinically reasonable, as patients on third-line treatments are expected to have longer disease duration than patients using second-line treatments.
Natural history	Natural history of T2DM was integrated in the model based on data from the UKPDS with a median follow-up time of 10.3 years.[11]	Appropriate.
Utilities	• Health state utility values were derived from the 2013 update to the CADTH Optimal Use Report.[13,14] • The utility at baseline of 0.753 was based on a US catalogue of EQ-5D scores from Sullivan et al. (2006)[32] • Disutilities associated with hypoglycemia were taken from a published study by Harris et al. (2014), which employed a time trade-off approach to estimate the utility values associated with non-severe and severe hypoglycemic events. All 1,696 patients who completed the analysis were Canadian.[16] • A disutility of –0.0061 kg/m^2 was applied in the base-case analysis for every unit of BMI above 25 kg/m^2 based on a study by Bagust and Beale (2005).[15] • The disutility associated with SMBG was from a published study (unspecified) that was used in a submission to the Scottish Medicines Consortium.[17]	Uncertainty with disutility associated with SMBG, as the source was not clearly specified.
Adverse events	The model included severe and non-severe hypoglycemic events: For second-line: Treatment-specific rates of overall hypoglycemia were derived from the insulin glargine arm of the ORIGIN trial by multiplying the base rate of non-severe hypoglycemia from the ORIGIN trial (of 1.3 events per patient per year) with overall hypoglycemia rate ratios from the NMA of the CADTH OU report on second-line therapies.[13,18] For third-line: Event rates for non-severe and severe hypoglycemia were based on data from the AWARD-2 trial.[6,12]	Appropriate.
Mortality	The model used the UKPDS Gompertz proportional hazards model to include background mortality.	The model also allows the use of Canadian life tables instead of Gompertz.

Data Input	Description of Data Source	Comment
Costs		
Drug	Drug costs associated with third-line treatment were derived from the Ontario Drug Benefit Formulary.[9]	The sources for the drug costs associated with second-line treatments were not identified.
Event	Costs associated with each diabetes complication were taken from the 2013 update to the CADTH OU reports and expressed in 2014 Canadian dollars by inflating the CADTH costs (in 2012 CAD) using the Health Component of the Canadian Consumer Price Index (index of 120.7 in 2012 versus 121.6 in December 2014).[13,14,33]	
Adverse events	Cost of severe hypoglycemia was based on the CADTH 2013 Second- and Third-Line OU reports.[13,14]	

BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life questionnaire; GLP-1 = glucagon-like peptide-1; NMA = network meta-analysis; OU = Optimal Use; SGLT2 = sodium/glucose cotransporter 2; SMBG = self-monitoring of blood glucose; T2DM = type 2 diabetes mellitus; UKPDS = United Kingdom Prospective Diabetes Study.

TABLE 22: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
The manufacturer indicated that because patients generally prefer oral therapies over injectable drugs, dulaglutide is expected to be used as an alternative to other injectable therapies (e.g., GLP-1 receptor analogues and insulins). With the exception of sulfonylurea, dulaglutide was not compared with oral antidiabetic drugs.	Likely appropriate, as indicated by the CDR clinical expert for this review. However, the clinical expert did note that it is possible for patients to replace daily oral treatments with once-weekly injectable drugs for the sake of convenience. Injectable options are unlikely to represent a significant proportion of utilization at second-line therapy. Based on reimbursement policies across CDR-participating jurisdictions, GLP-1 analogues are not listed for second- and third-line therapy; therefore, they do not represent a policy-relevant comparator.
The model was set to exclude the effect of BMI as a clinical driver of diabetes-related complications (notably as a risk factor for congestive heart failure) when disutility for BMI increase was applied, alleviating concerns of double-counting the effect of BMI on health-related quality of life.	Appropriate. However, while assessing the analyses that compared dulaglutide to insulin glargine based on efficacy data from the AWARD-2 trial, CDR noted that the model was in fact set to include the effects of BMI as a driver of clinical complications (i.e., the model was double-counting the effects of BMI increase).
A disutility of 0.0058 per year was assumed for each additional SMBG test per week. The reported disutility of –0.0058 was converted to a weekly disutility by dividing by 52 to give –0.0001115 per additional test and sensitivity analyses were performed around the use of the utility (and the frequency of SMBG testing).	Inappropriate. The disutility was based on an unspecified study that was used in a submission to the Scottish Medicines Consortium.[17] Sufficient information on how the disutility was elicited, calculated, and validated was not provided by the manufacturer.
For insulin-naive patients (i.e., those in the analyses of sulfonylurea or GLP-1 analogues), it was assumed that patients would intensify therapy to a basal-only insulin regimen when the individual patient A1C reached 9%.	Appropriate.

Assumption	Comment
For patients previously on insulin (i.e., those in the analyses of basal or biphasic insulin), it was assumed that patients would intensify therapy to a basal-bolus insulin regimen when the individual patient A1C reached 9%.	Appropriate
Mild or moderate hypoglycemic events required no health care resource use and, as such, had no associated costs.	Appropriate
Utilization of UKPDS 68 risk equations: The UKPDS 68 equations comprise a series of 7 Weibull proportional hazards models derived from a cohort of 5,102 diabetic patients, aged 25 to 65 years in the UK, from the UKPDS,[11] which ran for 20 years (1977 to 1997) for prediction of cardiovascular events.	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 since the UKPDS data were collected.[19,20]
A1C predicts cardiovascular events: Because the model was based on equations from the UKPDS 68 outcomes study, it inherently assumes that reductions in A1C levels are associated with reduced cardiovascular and other macrovascular events, and microvascular events.	The relationship between A1C and macrovascular events has been debated, and is further called into question by large trials powered to detect CV outcomes showing that some antidiabetic drug classes may reduce the risk of CV outcomes,[23] while others do not.[24] The available evidence also shows reduction in microvascular events only in patients with aggressive reductions in A1C.[19] However, the limitations of A1C in predicting microvascular and macrovascular outcomes are inherent in all cost-effectiveness modelling exercises for T2DM. Most guidelines no longer recommend aggressive reductions in A1C for diabetic patients, due to potentially increased risk of hypoglycemia.[19,20]
Modelling of future events: The economic evaluation relied on short-term clinical data (trial durations between 26 and 76 weeks)[5,6,12] to model and predict the costs and incidence of complications over a 40-year time horizon.	The lack of evidence demonstrating that short-term effects can be sustained over the long term casts uncertainty on the validity of the results of the model. However, this is a feature of all cost-effectiveness modelling exercises for T2DM.

A1C = glycated hemoglobin; BMI = body mass index; CDR = CADTH Common Drug Review; CV = cardiovascular; GLP-1 = glucagon-like peptide-1; SMBG = self-monitoring of blood glucose; T2DM = type 2 diabetes mellitus; UKPDS = United Kingdom Prospective Diabetes Study.

Manufacturer's Results

Second-Line Therapy

For the analyses of dulaglutide compared with liraglutide 1.8 mg as add-on treatment to metformin (i.e., second-line therapy) based on the AWARD-6 trial, dulaglutide 1.5 mg resulted in QALY gains of 0.01 and was associated with a reduction in total costs of $1,811, resulting in dulaglutide 1.5 mg dominating liraglutide 1.8 mg (Table 23).

TABLE 23: MANUFACTURER BASE-CASE RESULTS IN SECOND-LINE — DULAGLUTIDE VERSUS LIRAGLUTIDE BASED ON AWARD-6

Add-On to Metformin	Total Cost ($)	Incremental Cost ($)	Total QALY	Incremental QALY	ICUR ($/QALY)
Dulaglutide 1.5 mg[a]	62,785		8.90		Dulaglutide dominated liraglutide
Liraglutide 1.8 mg	65,596	–1,811	8.89	0.01	

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
[a] Dulaglutide 0.75 mg was not studied in the AWARD-6 trial.[5,12]
Source: Adapted from manufacturer submission for dulaglutide as second-line treatment: Table 19 (page 36).[3]

When compared with sulfonylureas, dulaglutide resulted in QALY gains of between 0.16 and 0.18 QALYS and incremental costs of $29,993 and $30,449 for dulaglutide 0.75 mg and 1.5 mg, respectively. The resulting ICURs for dulaglutide compared with sulfonylureas were $185,013 per QALY and $165,971 per QALY for dulaglutide 0.75 mg and 1.5 mg, respectively (Table 24).

TABLE 24: MANUFACTURER BASE-CASE RESULTS IN SECOND-LINE — DULAGLUTIDE VERSUS SULFONYLUREA BASED ON NETWORK META-ANALYSIS

Add-On to Metformin	Total Cost ($)	Incremental Cost ($)	Total QALY	Incremental QALY	ICUR ($/QALY)
Dulaglutide 0.75 mg	62,801		8.94		
Sulfonylurea (gliclazide)	32,808	29,993	8.78	0.16	185,013
Dulaglutide 1.5 mg	63,257		8.97		
Sulfonylurea (gliclazide)	32,808	30,449	8.78	0.18	165,971

ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer submission for dulaglutide as second-line treatment: Tables 17 (page 33) and 18 (page 35).[3]

Based on clinical inputs from the NMA, the comparison of dulaglutide 0.75 mg and 1.5 mg resulted in QALY losses of 0.03 and 0.005 and reductions in costs of $2,263 to $1,806, respectively, compared with other GLP-1 analogues as a class. This resulted in dulaglutide being less costly and less effective than the GLP-1 analogue class (Table 25).

TABLE 25: MANUFACTURER BASE -CASE RESULTS IN SECOND-LINE — DULAGLUTIDE VERSUS GLP-1 ANALOGUE CLASS BASED ON NETWORK META-ANALYSIS

Add-On to Metformin	Total Cost ($)	Incremental Cost ($)	Total QALY	Incremental QALY	ICUR ($/QALY)
Dulaglutide 0.75 mg	62,801		8.94		Dulaglutide less costly and less effective
GLP-1 analogue class	65,063	–2,263	8.97	–0.03	
Dulaglutide 1.5 mg	63,257		8.97		Dulaglutide less costly and less effective
GLP-1 analogue class	65,063	–1,806	8.97	–0.005	

GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer submission for dulaglutide as second-line treatment: Tables 20 (page 38) and 21 (page 39).[3]

When compared with basal insulin based on clinical inputs from the NMA, dulaglutide resulted in gains of between 0.11 and 0.13 QALYs at an additional cost of between $13,636 and $13,953. This yielded ICURs of $126,049 per QALY for dulaglutide 0.75 mg and $104,402 per QALY for dulaglutide 1.5 mg compared to basal insulin (Table 26).

TABLE 26: MANUFACTURER BASE-CASE RESULTS IN SECOND-LINE — DULAGLUTIDE VERSUS BASAL INSULIN BASED ON NETWORK META-ANALYSIS

Add-On to Metformin	Total Cost ($)	Incremental Cost ($)	Total QALY	Incremental QALY	ICUR ($/QALY)
Dulaglutide 0.75 mg	63,057		8.94		
Basal insulin (insulin glargine)	49,421	13,636	8.83	0.11	126,049
Dulaglutide 1.5 mg	63,374		8.96		
Basal insulin (insulin glargine)	49,421	13,953	8.83	0.13	104,402

ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-years.
Source: Adapted from manufacturer submission for dulaglutide as second-line treatment: Tables 22 (page 41) and 23 (page 42).[3]

Finally, when compared with biphasic insulin as second-line therapy, dulaglutide 0.75 mg resulted in a gain of 0.31 QALYs and an increased cost of $2,828, yielding an ICUR of $9,101 per QALY. For dulaglutide 1.5 mg compared with biphasic insulin, 0.34 QALYs were gained at an incremental cost of $3,145, resulting in an ICUR of $9,356 per QALY (Table 27).

TABLE 27: MANUFACTURER BASE-CASE RESULTS IN SECOND-LINE — DULAGLUTIDE VERSUS BIPHASIC INSULIN BASED ON NETWORK META-ANALYSIS

Add-On to Metformin	Total Cost ($)	Incremental Cost ($)	Total QALY	Incremental QALY	ICUR ($/QALY)
Dulaglutide 0.75 mg	63,057		8.94		
Biphasic insulin	60,229	2,828	8.63	0.31	9,101
Dulaglutide 1.5 mg	63,374		8.96		
Biphasic insulin	60,229	3,145	8.63	0.34	9,356

ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer submission for dulaglutide as second-line treatment: Tables 24 (page 44) and 25 (page 45).[3]

Third-Line Therapy

For the analyses of dulaglutide as add-on treatment to metformin plus a sulfonylurea (i.e., third-line therapy), the comparison of dulaglutide 0.75 mg with insulin glargine based on clinical inputs from the AWARD-2 trial resulted in QALY gains of 0.21 with incremental costs of $14,120, resulting in an ICUR of $66,674 per QALY. For dulaglutide 1.5 mg compared with insulin glargine based on the AWARD-2 trial, there was a gain of 0.27 QALYs at an incremental cost of $15,100, resulting in an ICUR of $56,016 per QALY (Table 28).

TABLE 28: MANUFACTURER BASE-CASE RESULTS IN THIRD-LINE — DULAGLUTIDE VERSUS INSULIN GLARGINE BASED ON AWARD-2

Add-On to Metformin Plus a Sulfonylurea	Total Cost ($)	Incremental Cost ($)	Total QALY	Incremental QALY	ICUR ($/QALY)
Dulaglutide 0.75 mg	60,417		9.01		
Insulin glargine	46,297	14,120	8.81	0.21	66,674
Dulaglutide 1.5 mg	61,397		9.08		
Insulin glargine	46,297	15,100	8.81	0.27	56,016

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer submission for dulaglutide as third-line treatment: Tables 14 and 15 (page 30).[4]

Based on clinical inputs from the NMA, the comparison of dulaglutide 0.75 mg and 1.5 mg with insulin glargine resulted in QALY gains of 0.19 and 0.22 at incremental costs of $11,537 and $12,271, respectively. This resulted in ICURs for dulaglutide 0.75 mg and 1.5 mg of $62,152 and $56,057 per QALY, respectively, compared to insulin glargine (Table 29).

TABLE 29: MANUFACTURER BASE-CASE RESULTS IN THIRD-LINE — DULAGLUTIDE VERSUS INSULIN GLARGINE BASED ON NETWORK META-ANALYSIS

Add-On to Metformin + a Sulfonylurea	Total Cost ($)	Incremental Cost ($)	Total QALY	Incremental QALY	ICUR ($/QALY)
Dulaglutide 0.75 mg	59,880		8.95		
Insulin glargine	48,343	11,537	8.76	0.19	62,152
Dulaglutide 1.5 mg	60,613		8.98		
Insulin glargine	48,343	12,271	8.76	0.22	56,057

ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life year.
Source: Adapted from manufacturer submission for dulaglutide as third-line treatment: Tables 23 (page 39) and 24 (page 40).[4]

When compared with biphasic insulin, dulaglutide resulted in QALY gains of 0.25 and 0.29 for dulaglutide 0.75 mg and 1.5 mg, respectively, at an additional cost of $2,731 and $3,394, respectively. This yielded ICURs of $10,820 per QALY for dulaglutide 0.75 mg and $11,740 per QALY for dulaglutide 1.5 mg compared with biphasic insulin (Table 30).

TABLE 30: MANUFACTURER BASE-CASE RESULTS IN THIRD-LINE — DULAGLUTIDE VERSUS BIPHASIC INSULIN BASED ON NETWORK META-ANALYSIS

Add-On to Metformin + a Sulfonylurea	Total Cost ($)	Incremental Cost ($)	Total QALY	Incremental QALY	ICUR ($/QALY)
Dulaglutide 0.75 mg	60,126		8.94		
Biphasic insulin	57,395	2,731	8.69	0.25	10,820
Dulaglutide 1.5 mg	60,789		8.98		
Biphasic insulin	57,395	3,394	8.69	0.29	11,740

ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life year.
Source: adapted from manufacturer submission for dulaglutide as third-line treatment. Tables 31 (page 47) and 32 (page 48).[4]

Finally, when compared with GLP-1 analogues as a class, dulaglutide 0.75 mg resulted in QALY gains of 0.05 and was associated with cost savings of $806, resulting in dulaglutide dominating the GLP-1 analogue class. For dulaglutide 1.5 mg compared with GLP-1 analogues, QALY gains of 0.09 were reported at cost savings of $143, resulting in dulaglutide 1.5 mg dominating GLP-1 analogues (Table 31).

TABLE 31: MANUFACTURER BASE-CASE RESULTS IN THIRD-LINE — DULAGLUTIDE VERSUS GLP-1 ANALOGUE CLASS BASED ON NETWORK META-ANALYSIS

Add-On to Metformin + a Sulfonylurea	Total Cost ($)	Incremental Cost ($)	Total QALY	Incremental QALY	ICUR ($/QALY)
Dulaglutide 0.75 mg	60,126		8.94		
GLP-1 analogue class	60,932	-806	8.89	0.05	dulaglutide dominated GLP-1
Dulaglutide 1.5 mg	60,789		8.98		
GLP-1 analogue class	60,932	-143	8.89	0.09	dulaglutide dominated GLP-1

GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; NMA = network meta-analysis; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer submission for dulaglutide as third-line treatment: Tables 33 and 34 (page 50).[4]

Manufacturer's Sensitivity Analyses

The manufacturer's pharmacoeconomic submission for the use of dulaglutide as add-on to metformin (i.e., second-line therapy) did not include information on whether sensitivity analyses were conducted, nor were any results provided. However, the manufacturer did plot cost-effectiveness scatter plots by grouping sequential patients into cohorts of 50 and plotting the mean incremental cost and QALYs for each group. The scatter plots were then used to generate cost-effectiveness acceptability curves showing the likelihoods of dulaglutide (0.75 mg and 1.5 mg) being cost-effective relative to the comparators over a range of willingness-to-pay thresholds.[3] Due to technical limitations with the submitted model, CDR was unable to recreate the manufacturer's cost-effectiveness acceptability curves or obtain the precise probabilities. Therefore, the results in Table 32 were derived from the figures provided in the manufacturer's submission.

TABLE 32: MANUFACTURER'S SUMMARY RESULTS OF THE PROBABILITY OF DULAGLUTIDE BEING COST-EFFECTIVE RELATIVE TO COMPARATORS FOR SECOND-LINE THERAPY

	Comparator	Probability of Being Cost-Effective at	
		$50,000 per QALY	$100,000 per QALY
Dulaglutide 0.75 mg	Sulfonylurea	0%	1%
	GLP-1 analogues (NMA)	76%	46%
	Basal insulin	0%	4%
	Biphasic insulin	100%	100%
Dulaglutide 1.5 mg	Sulfonylurea	0%	5%
	Liraglutide 1.8 mg (AWARD-6)	86%	86%
	GLP-1 analogues (NMA)	95%	75%
	Basal insulin	1%	20%
	Biphasic insulin	100%	100%

GLP-1 = glucagon-like peptide-1; NMA = network meta-analysis; QALY = quality-adjusted life-year.
Source: adapted from manufacturer submission for dulaglutide as second-line treatment.[3]

For the analyses of dulaglutide as add-on to metformin plus a sulfonylurea (i.e., third-line therapy) compared with insulin glargine, the manufacturer conducted one-way sensitivity analyses around the following key model parameters:

- Time horizon (varied from 40 years to 10, 20, and 30 years)
- Cost of complications
- Key drivers of clinical benefit (A1C, SBP, serum lipids, BMI, and hypoglycemia rates)
- Hypoglycemia disutilities
- Impact of high BMI on quality of life
- Impact of SMBG on quality of life
- Impact of high BMI and SMBG on quality of life
- Doses of insulin products
- Treatment discontinuation

Sensitivity analyses were conducted only around the results of dulaglutide compared with insulin glargine using efficacy data from both the AWARD-2 trial and NMA. The results were most sensitive to the inclusion of A1C and BMI treatment effects in the dulaglutide arm, and the choice (and use) of utilities associated with hypoglycemic events, SMBG testing, and excess BMI.

For the third-line setting, the manufacturer also plotted cost-effectiveness scatter plots by grouping sequential patients into cohorts of 50 and plotting the mean incremental costs and QALYs for each group. The scatter plots were also used to generate cost-effectiveness acceptability curves showing the likelihoods of dulaglutide (0.75 mg and 1.5 mg) being cost-effective relative to the comparators over a range of willingness-to-pay thresholds.[4] As with the second-line analysis, due to technical limitations with the submitted model, CDR was unable to recreate the manufacturer's cost-effectiveness acceptability curves or obtain the precise probabilities for dulaglutide in third-line therapy. Therefore, the results in Table 33 were derived from the figures provided in the manufacturer's submission.

TABLE 33: MANUFACTURER SUMMARY RESULTS OF THE PROBABILITY OF DULAGLUTIDE BEING COST-EFFECTIVE RELATIVE TO COMPARATORS FOR THIRD-LINE THERAPY

	Comparator	Probability of Being Cost-Effective at	
		$50,000 per QALY	$100,000 per QALY
Dulaglutide 0.75 mg	Insulin glargine (AWARD-2)	12%	91%
	Insulin glargine (NMA)	20%	90%
	GLP-1 analogues	87%	85%
	Basal insulin	NR	NR
	Biphasic insulin	99%	100%
Dulaglutide 1.5 mg	Insulin glargine (AWARD-2)	26%	94%
	Insulin glargine (NMA)	20%	90%
	GLP-1 analogues (NMA)	91%	92%
	Basal insulin	NR	NR
	Biphasic insulin	99%	100%

GLP-1 = glucagon-like peptide-1; NMA = network meta-analysis; NR = not reported by manufacturer; QALY = quality-adjusted life-year.
Source: Adapted from manufacturer submission for dulaglutide as third-line treatment.[4]

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