CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

DULAGLUTIDE
(Trulicity — Eli Lilly Canada Inc.)
Indication: Type 2 Diabetes

Recommendation I
The CADTH Canadian Drug Expert Committee (CDEC) recommends that dulaglutide be reimbursed for the treatment of adults with type 2 diabetes mellitus in combination with metformin to improve glycemic control, if the following condition is met:

Condition:
- Drug plan cost not to exceed that of the least costly pharmacotherapy reimbursed in combination with metformin.

Reasons for the Recommendation:
- Two phase 3 multi-centre, active-controlled, non-inferiority trials in patients on ≥ 1,500 mg/day of metformin found that dulaglutide 0.75 mg and 1.5 mg administered subcutaneously (SC) once weekly was likely clinically superior to sitagliptin 100 mg orally daily at reducing glycated hemoglobin (A1C) up to 104 weeks compared with baseline, and that dulaglutide 1.5 mg SC weekly was statistically non-inferior to liraglutide 1.8 mg SC daily at 26 weeks.
- Dulaglutide was not cost-effective at the submitted price when compared with relevant second-line therapeutic options for type 2 diabetes mellitus used in combination with metformin. Furthermore, there are limited direct clinical comparative data with other less costly medications typically used as a second-line therapy. The CADTH Common Drug Review (CDR) base-case incremental cost-utility ratios (ICURs) were $278,000 and $1,500,000 compared with a sulfonylurea and a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Recommendation II
CDEC recommends that dulaglutide be reimbursed for the treatment of adults with type 2 diabetes mellitus in combination with metformin and a sulfonylurea to improve glycemic control if the following condition is met:

Condition:

- Drug plan cost not to exceed the least costly pharmacotherapy reimbursed in combination with metformin and a sulfonylurea.

Reasons for the Recommendation:

- In one phase 3 multi-centre, active-controlled, non-inferiority trial in patients on ≥ 1,500 mg/day of metformin and ≥ 4 mg/day of glimepiride, dulaglutide 0.75 mg SC weekly was found to be non-inferior to insulin glargine, and dulaglutide 1.5 mg SC weekly was found to be statistically superior to insulin glargine for reducing A1C up to 78 weeks compared with baseline when used in combination with metformin and a sulfonylurea.
- Dulaglutide was not cost-effective at the submitted price when compared with relevant comparators as a third-line drug. The CDR base-case ICURs were $192,000 to $243,000 per quality-adjusted life-year (QALY) compared with insulin NPH, and $123,000 to $182,000 per QALY compared with insulin glargine.

Of Note:

CDEC noted that although a once-weekly injection of dulaglutide compared with once-daily insulin administration may be more convenient for some patients, there were limited data in the clinical trials to support this additional value.

Research Gaps:

CDEC noted the following research gap:

- The value to patients — in terms of approved adherence and/or health-related quality of life (HRQoL) for the once-weekly SC administration of dulaglutide as compared with daily administration of the most relevant alternatives — is uncertain and requires further study.

Background:

Dulaglutide is a glucagon-like peptide-1 (GLP-1) agonist indicated for use in patients with type 2 diabetes to improve glycemic control in combination with (1) diet and exercise, in patients for whom metformin is inappropriate due to contraindication or intolerance; (2) metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control; (3) metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control; and (4) 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.

This CDR submission is for the use of dulaglutide as second-line treatment (i.e., in combination with metformin alone) and as third-line treatment (i.e., in combination with metformin and a sulfonylurea).

Summary of CDEC Considerations:

The Committee considered the following information prepared by CDR: a systematic review of randomized controlled trials of dulaglutide, a literature review and critique of indirect treatment

comparisons, a critique of the manufacturer-submitted pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information:
One patient group, the Canadian Diabetes Association, responded to the CDR call for patient input. Information for the patient input submission was obtained from online surveys. The following is a summary of information provided by the patient group:

- Diabetes has a negative psychological and emotional impact on the lives of patients and their caregivers.
- Many patients using currently available therapies fail to achieve optimal glycemic control.
- Poorly controlled type 2 diabetes can result in serious long-term complications, such as blindness, heart disease, kidney problems, nerve damage, and erectile dysfunction.
- In addition to controlling blood glucose without hypoglycemia, the aspects of diabetes management that are most important to patients include avoiding weight gain, reducing high blood pressure, and avoiding fluid retention, gastrointestinal effects, and urinary tract infections.
- Patients hope that new medications will offer affordable and accessible treatments, better diabetes control with minimal or no side effects (especially hypoglycemia), improved life and life expectancy without diabetes complications, less frequent medications with fewer needles and testing, weight loss or prevention of weight gain, and a cure for diabetes.

Clinical Trials

Second-line treatment

The CDR systematic review included two phase 3 multi-centre, active-controlled, non-inferiority trials. AWARD-5 was an adaptive, inferentially seamless phase 2/3 study that randomized 1,098 participants to one of four primary treatment arms — dulaglutide 0.75 mg, dulaglutide 1.5 mg, sitagliptin 100 mg, and placebo/sitagliptin for 24 months. AWARD-6 was an open-label study that randomized 599 participants to receive dulaglutide 1.5 mg or liraglutide 1.8 mg for 26 weeks.

Third-line treatment

The CDR systematic review included one phase 3 multi-centre, active-controlled, non-inferiority trial. AWARD-2 was an open-label trial, although double-blind with respect to the dulaglutide assignments, which randomized 810 participants to dulaglutide 0.75 mg, dulaglutide 1.5 mg, or insulin glargine for 78 weeks.

Outcomes
The following efficacy outcomes were defined a priori in the CDR systematic review protocol:
- Mortality
- Diabetes-related morbidity (macrovascular, microvascular)
- Glycemic control (A1C, fasting plasma glucose [FPG])
- HRQoL

- Body weight
- Blood pressure
- Treatment satisfaction and/or preference
- Fear of injections
- Health care resource utilization.

The following harms outcomes were defined a priori in the CDR systematic review protocol:

- Adverse events (AEs)
- Serious AEs (SAEs)
- Withdrawals due to AEs
- Notable harms — hypoglycemia, injection-site reactions, pancreatitis, and pancreatic and thyroid cancers.

Efficacy

Second-line treatment

In AWARD-5, among participants randomized during stage 1 or 2, there was a greater reduction from baseline in A1C at week 52 in the dulaglutide 0.75 mg and 1.5 mg groups compared with the sitagliptin group: least squares mean difference (LS MD) (nominal 95% confidence interval [CI]) of –0.47 (–0.63 to –0.31) ($P < 0.001$) and –0.71 (–0.87 to –0.55) ($P < 0.001$), respectively. In AWARD-6, dulaglutide 1.5 mg was statistically non-inferior to liraglutide 1.8 mg with respect to the change in A1C from baseline to week 26, as indicated by an LS MD (nominal 95% CI) of –0.06 (–0.19 to 0.07) ($P < 0.001$). The results were consistent across the different statistical models, populations used, and at the longest follow-up time point. Further, there did not seem to be any important interactions between subgroups of interest and treatment across the two trials. In AWARD-5, at 52 weeks, more participants receiving dulaglutide 0.75 mg (48.8%) and 1.5 mg (57.6%) achieved A1C < 7.0% than those receiving sitagliptin (33.0%) ($P < 0.001$). In AWARD-6, at 26 weeks, there was no statistically significant difference in the percentage of participants who achieved A1C < 7.0% between those receiving dulaglutide 1.5 mg (68.3%) and liraglutide 1.8 mg (67.9%).

In AWARD-5, participants receiving dulaglutide 0.75 mg and 1.5 mg experienced greater reduction in FPG at week 52 than those receiving sitagliptin: LS MD (95% CI) of –0.73 mmol/L (–1.07 to –0.39) ($P < 0.001$) and –1.47 mmol/L (–1.82 to –1.13) ($P < 0.001$), respectively. In AWARD-6, there was no statistically significant difference in reduction from baseline in FPG at week 26 between the dulaglutide 1.5 mg and liraglutide 1.8 mg groups: LS MD (95% CI) of –0.03 mmol/L (–0.32 to 0.25) ($P = 0.828$).

In AWARD-5, participants receiving dulaglutide 0.75 mg and 1.5 mg lost more weight at week 52 than those receiving sitagliptin: LS MD (95% CI) of –1.07 kg (–1.65 to –0.48) ($P < 0.001$) and –1.50 kg (–2.08 to –0.92) ($P < 0.001$), respectively. In AWARD-6, participants receiving dulaglutide 1.5 mg lost less weight at week 26 than those receiving liraglutide 1.8 mg: LS MD (95% CI) of 0.71 kg (0.17 to 1.26) ($P < 0.001$).

In AWARD-5, although statistical significance was not tested, there appeared to be a small increase (from baseline to week 52) in each of the mean scores of the EuroQol 5-Dimensions Health-Related Quality of Life questionnaire (EQ-5D) visual analogue scale (VAS), EQ-5D UK

and US population-based Index Scores, and the total score on the Impact of Weight on Quality of Life–Lite (IWQOL-Lite). In AWARD-6, there were no statistically significant differences in changes in HRQoL at week 26 between participants receiving dulaglutide or liraglutide.

In AWARD-5, there were a total of four deaths, of which three were cardiovascular (CV) in nature — one each in the dulaglutide 1.5 mg, sitagliptin, and placebo/sitagliptin arms. No deaths were reported in AWARD-6.

In AWARD-5, four participants experienced treatment-emergent diabetic retinopathy — one receiving dulaglutide 0.75 mg, two receiving dulaglutide 1.5 mg, and one receiving sitagliptin. More participants receiving dulaglutide 1.5 mg experienced treatment-emergent diabetic nephropathy than individuals in other treatment groups, while more participants receiving dulaglutide 0.75 mg experienced treatment-emergent diabetic neuropathy than individuals in other treatment groups. Furthermore, a total of four patients suffered a non-fatal stroke or a transient ischemic attack (TIA), of whom three were receiving dulaglutide 0.75 mg and one was receiving dulaglutide 1.5 mg. Moreover, a total of six patients suffered a non-fatal myocardial infarction (MI) in this study. In AWARD-6, one participant receiving dulaglutide 1.5 mg experienced treatment-emergent diabetic retinopathy, while another in the same group experienced diabetic neuropathy, and one participant receiving liraglutide 1.8 mg suffered a non-fatal MI.

In AWARD-5, there were no statistically significant differences observed across the treatment groups at 52 weeks in the number of participants reporting at least one emergency room (ER) visit and no ER visits since the last visit. AWARD-6 did not assess health care resource utilization.

A manufacturer-submitted network meta-analysis (NMA) suggested clinically important reductions in A1C with dulaglutide 0.75 mg or 1.5 mg versus DPP-4 inhibitors, sodium/glucose cotransporter 2 (SGLT2) inhibitors, thiazolidinediones, acarbose, and meglitinides; no differences were found against other GLP-1 agonists, sulfonylureas, and insulin. Another NMA (identified through the literature search) evaluated the relative efficacy and safety of various GLP-1 agonists and found no within-class differences.

Third-line treatment

In AWARD-2, at 52 weeks, with respect to the primary efficacy end point of the change in A1C from baseline, dulaglutide 0.75 mg was statistically non-inferior to insulin glargine — LS MD (nominal 95% CI) of –0.13 (–0.29 to 0.02) ($P < 0.001$) — and dulaglutide 1.5 mg was statistically superior to insulin glargine — LS MD (nominal 95% CI) of –0.45 (–0.60 to –0.29) ($P < 0.001$). The above results were consistent across the different statistical models, populations used, and at 104 weeks. There was a statistically significant interaction between treatment and duration of diabetes at baseline, specifically with respect to a difference in change in A1C from baseline to week 52. Further, there was no statistically significant difference in the percentage of participants who achieved A1C < 7.0% between those receiving dulaglutide 0.75 mg (37.1%) and insulin glargine (30.9%). There were, however, significantly more participants receiving dulaglutide 1.5 mg (53.2%) than those receiving insulin glargine who achieved A1C < 7.0%.

Participants receiving insulin glargine experienced greater reduction in FPG at week 52 than those receiving dulaglutide 0.75 mg (LS MD not reported), although the difference was not statistically significant when compared with those receiving dulaglutide 1.5 mg.

Participants receiving dulaglutide 0.75 mg and 1.5 mg lost more weight at week 52 than those receiving insulin glargine — LS MD not reported, but the 95% CIs ranged from 2.17 kg to 3.36 kg ($P < 0.001$), and 2.71 kg to 3.90 kg ($P < 0.001$) for the respective comparisons.

There were no statistically significant differences in reduction of blood pressure at week 52 between participants receiving dulaglutide and insulin glargine.

Participants receiving dulaglutide experienced little or no change in HRQoL, whereas those receiving insulin glargine experienced a slight decrease, thus resulting in a statistically greater decrease in HRQoL with insulin glargine relative to dulaglutide.

There were a total of three deaths, of which two were CV in nature — one each in the dulaglutide 0.75 mg and insulin glargine treatment arms.

Four participants (all receiving dulaglutide 0.75 mg) experienced treatment-emergent diabetic retinopathy, while two individuals (both receiving insulin glargine) experienced treatment-emergent diabetic neuropathy. More participants receiving insulin glargine experienced a non-fatal stroke or TIA or MI than those in the other treatment groups.

A manufacturer-submitted NMA suggested clinically important reductions in A1C with dulaglutide 0.75 mg or 1.5 mg versus DPP-4 inhibitors and thiazolidinediones; no differences were found against other GLP-1 agonists, SGLT2 inhibitors, basal insulin, biphasic insulin, and bolus insulin.

Harms (Safety and Tolerability)

Second-line treatment

In AWARD-5, over the entire 24-month treatment period, at least 75% of participants in each treatment group experienced a treatment-emergent AE. A greater proportion of participants receiving dulaglutide 0.75 mg (84.4%) and 1.5 mg (85.2%) experienced an AE than those receiving sitagliptin (76.8%). The two most common AEs across the four treatment arms were nasopharyngitis and hyperglycemia. A greater proportion of participants receiving either dose of dulaglutide experienced nausea, diarrhea, and vomiting than those in the other treatment groups. A smaller proportion of participants receiving dulaglutide 1.5 mg experienced hyperglycemia than those in the other treatment groups. In AWARD-6, over the entire 26-week treatment period, more than 60% of participants in each treatment group experienced an AE, with a seemingly equal proportion in each arm. The most common AE across the treatment arms was nausea, followed by diarrhea, headache, and vomiting. There were no differences in the occurrence of AEs between participants receiving dulaglutide 1.5 mg and liraglutide 1.8 mg.

In AWARD-5, a smaller proportion of participants receiving dulaglutide 0.75 mg (7.5%) experienced an SAE than those receiving dulaglutide 1.5 mg (11.8%), sitagliptin (10.2%), and placebo/sitagliptin (9.0%) over 24 months. In AWARD-6, a greater proportion of participants

receiving liraglutide 1.8 mg (3.7%) experienced an SAE than those receiving dulaglutide 1.5 mg (1.7%) over 26 weeks.

In AWARD-5, at least 20% of participants in each treatment group discontinued from the study prior to 24 months, due to a death or an AE, with an approximately equal proportion of such withdrawals in each group. In AWARD-6, a smaller proportion of participants receiving dulaglutide 1.5 mg (2.0%) experienced an AE that led to discontinuation of study treatment versus those receiving liraglutide 1.8 mg (4.7%). However, a greater proportion of participants receiving dulaglutide 1.5 mg (4.3%) discontinued from the study prior to 26 weeks due to an AE, when compared with those receiving liraglutide 1.8 mg (1.7%).

In AWARD-5, over the entire 24-month treatment period, the proportion of participants who experienced hypoglycemia (plasma glucose [PG] ≤ 3.9 mmol/L) ranged from 4.5% (placebo/sitagliptin) to 12.8% (dulaglutide 1.5 mg). A greater proportion of participants in the dulaglutide 1.5 mg treatment group experienced hypoglycemia and documented symptomatic hypoglycemia than those in the dulaglutide 0.75 mg group. There were no differences in the proportion of participants who experienced other notable harms — specifically, injection-site reactions, pancreatitis, and pancreatic and thyroid cancer — across the four treatment groups. In AWARD-6, over the entire 26-week treatment period, a greater proportion of participants receiving dulaglutide 1.5 mg (8.7%) experienced hypoglycemia than those receiving liraglutide 1.8 mg (5.7%). There did not appear to be any differences in the proportion of participants who experienced other notable harms across the two treatment groups.

Third-line treatment

In AWARD-2, over the entire 78-week treatment period, approximately 70% of participants in each treatment group experienced an AE. The most common AEs across the treatment arms were diarrhea and nausea, both of which occurred more commonly among participants receiving either dose of dulaglutide versus insulin glargine. A greater proportion of participants receiving the higher dose of dulaglutide experienced AEs, such as diarrhea, nausea, nasopharyngitis, and headache, than those receiving the lower dose. Moreover, a greater proportion of participants receiving insulin glargine experienced nasopharyngitis than those receiving either dose of dulaglutide.

At least 10% of participants in each treatment group experienced an SAE over 78 weeks. A greater proportion of participants receiving insulin glargine (12.2%) experienced an SAE than those receiving either dulaglutide dose (dulaglutide 0.75 mg: 10.3%; dulaglutide 1.5 mg: 11.7%).

No participant receiving insulin glargine discontinued from study medication due to an AE; this is in contrast to approximately 6% of participants who did so while receiving either of the dulaglutide doses. A greater proportion of participants who received either dose of dulaglutide discontinued from the study due to an AE prior to 78 weeks when compared with those receiving insulin glargine.

More than half the participants in each treatment group experienced hypoglycemia (PG ≤ 3.9 mmol/L), with a greater proportion of those receiving insulin glargine (71.4%) than either dulaglutide dose (56.6% for 0.75 mg, 58.6% for 1.5 mg). This trend was consistent with those observed with respect to the occurrence of documented symptomatic hypoglycemia and

nocturnal hypoglycemia across the three treatment groups. There did not appear to be any differences in the proportion of participants who experienced other notable harms across the groups.

Cost and Cost-Effectiveness

At the submitted price of $47.95 per 0.75 mg/0.5 mL or 1.5 mg/0.5 mL pre-filled pen, dulaglutide ($6.85 daily) is similar in price to the GLP-1 agonists liraglutide 1.8 mg/day ($6.85 daily) and exenatide (Bydureon) 2 mg once weekly ($6.85 daily), but more expensive than liraglutide 1.2 mg ($4.57 daily), exenatide (Byetta) 5 mcg or 10 mcg twice daily ($3.99 daily), DPP-4 inhibitors ($2.25 to $2.98 daily), SGLT2 inhibitors ($2.45 to $2.70 daily), insulins ($2.26 to $6.19 per mL), metformin ($0.18 daily), and sulfonylureas (up to $0.43 daily).

The manufacturer submitted a cost-utility analysis of dulaglutide as add-on therapy to metformin or metformin and a sulfonylurea using the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model. 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 GLP-1 analogues. For dulaglutide in combination with metformin and a sulfonylurea (i.e., third-line therapy), dulaglutide 0.75 mg and 1.5 mg were compared to insulin glargine, biphasic insulins, and other GLP-1 analogues. The time horizon was lifetime (up to 40 years), and the analysis was conducted from the Canadian public payer perspective. Clinical data for the comparisons of interest were obtained from trials of dulaglutide or NMAs.

In the second-line setting, ICURs for dulaglutide were between $104,402 and $126,049 per QALY compared with basal insulin; $9,101 and $9,356 per QALY compared with biphasic insulin; and $165,971 and $185,013 per QALY compared with sulfonylureas. Compared with other GLP-1 analogues, dulaglutide was less costly and associated with either slightly greater or lesser benefits depending upon the source of the clinical data. In the third-line setting, ICURs for dulaglutide were between $56,016 and $66,674 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 other GLP-1 analogues.

CDR identified the following key limitations with the manufacturer's economic submission:

- 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 significant differences in clinical outcomes reported in the manufacturer-submitted NMA. In addition, CDR identified a lower publicly available price for liraglutide than the value used by the manufacturer.
- Uncertainty in utility values: The manufacturer used a higher value than previous CADTH analyses for the disutility associated with increased body mass index. The manufacturer also applied a disutility to self-monitoring of blood glucose (SMBG) derived from an unspecified source that was of uncertain validity.
- Choice of basal insulin: The manufacturer compared dulaglutide with insulin glargine only; however, CADTH recommends insulin NPH for most patients requiring third-line therapy. Furthermore, some CDR-participating jurisdictions reimburse insulin glargine on a restricted basis, after a trial of insulin NPH.
- 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.

CDR's base-case analyses for second- and third-line therapy incorporated DPP-4 inhibitors and SGLT2 inhibitors, used a revised price for liraglutide, incorporated the disutility for weight gain employed in previous CADTH reports, and removed the disutility associated with SMBG.

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
- $192,000 to $243,000 per QALY compared with insulin NPH
- 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.

For second-line therapy compared with sulfonylureas, and for second- and third-line therapy compared with DPP-4 inhibitors or SGLT2 inhibitors, dulaglutide price reductions of 50% or more would be required for ICURs to fall in a range that may be considered cost-effective. A price reduction 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.

CDEC Members:
Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

May 18, 2016 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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