CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

DAPAGLIFLOZIN
(Forxiga — AstraZeneca Canada Inc.)
Indication: Type 2 Diabetes

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that dapagliflozin be listed for use in patients with type 2 diabetes mellitus to improve glycemic control, if the clinical criteria and condition are met for any one of the following four scenarios:

Clinical criteria

1. Added on to metformin for patients:
   - Who have inadequate glycemic control on metformin
   - Who have a contraindication or intolerance to a sulfonylurea
   - For whom insulin is not an option.
2. Added on to a sulfonylurea for patients:
   - Who have inadequate glycemic control on a sulfonylurea
   - Who have a contraindication or intolerance to metformin
   - For whom insulin is not an option.
3. Added on to insulin in combination with metformin for patients with inadequate glycemic control on insulin with metformin.
4. Added on to insulin without metformin for patients with the following:
   - Inadequate glycemic control on insulin
   - Contraindication or intolerance to metformin.

Condition

- Drug plan cost of treatment with dapagliflozin should not exceed the drug plan cost of treatment with the least costly option from within the sodium-glucose cotransporter-2 (SGLT-2) inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor classes.

Of Note:

- CDEC noted that the most appropriate comparator for dapagliflozin may vary across the CADTH Common Drug Review (CDR)-participating drug plans, due to differences in the reimbursement status of SGLT-2 inhibitors and DPP-4 inhibitors.
- A large number of new agents have become available since the CADTH Therapeutic Review was last updated. At the time of this review, no other SGLT-2 inhibitors have been reviewed through the CDR process for dual therapy (i.e., in combination with metformin or a sulfonylurea) or for use in combination with insulin. CDEC noted that there is uncertainty regarding the role of dapagliflozin and other SGLT-2 inhibitors for these indications.

- CDEC noted that an updated CADTH therapeutic review is required to accurately evaluate the comparative clinical benefit and cost-effectiveness of SGLT-2 inhibitors, including dapagliflozin, relative to other available antihyperglycemic agents, particularly DPP-4 inhibitors.

Reasons for the Recommendation:

1. One randomized controlled trial (RCT) (Study 4 [N = 801]) demonstrated that dapagliflozin was non-inferior to glipizide for improving glycemic control, and superior to it for reducing body weight and blood pressure.
2. Dapagliflozin was superior to placebo for improving glycemic control when taken in combination with metformin (Studies 12 [N = 180] and 14 [N = 546]), a sulfonylurea (Study 5 [N = 438]), and insulin (Study 6 [N = 598]).
3. Reanalyses of the manufacturer's pharmacoeconomic model conducted by CDR suggested that dapagliflozin is associated with the following incremental cost-utility ratios (ICURs): $25,939 to $342,374 per quality-adjusted life-year (QALY) compared with a sulfonylurea as add-on to metformin; $12,453 to $1,021,404 per QALY compared with a DPP-4 inhibitor as add-on to a sulfonylurea; and $2,486 to $53,123 per QALY compared with a DPP-4 inhibitor as add-on to insulin.

Background:

Dapagliflozin is an SGLT-2 inhibitor indicated for patients with type 2 diabetes to improve glycemic control as monotherapy, with metformin, with a sulfonylurea, and insulin (alone or with metformin). This CDR submission is for use in combination with metformin, a sulfonylurea, or with insulin.

Dapagliflozin is available in 5 mg and 10 mg tablets. The recommended starting dose is 5 mg once daily, which can be increased to 10 mg daily in patients who tolerate 5 mg once daily and who require additional glycemic control.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of dapagliflozin, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients with type 2 diabetes.

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:

- 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.
- Fluctuations in blood sugar can negatively affect patients' ability to work and participate in social and family activities, and can interrupt their normal activities of daily living.

- Diabetes, and the related stigma, is associated with a psychological and emotional burden for patients.
- Many of the currently available therapies can cause significant weight gain, hypoglycemia, and other adverse effects.

Clinical Trials

The CDR systematic review included six multi-centre, double-blind, RCTs. Four of the studies were conducted in patients with inadequate glycemic control with metformin (Studies 4, 12, 14, and 18), one study enrolled patients with inadequate glycemic control with a sulfonylurea (Study 5), and one study enrolled patients with inadequate glycemic control with insulin (Study 6). Key characteristics of the studies include the following:

- Study 4 (N = 801): A 52-week non-inferiority study comparing dapagliflozin (2.5 mg, 5 mg, or 10 mg) with glipizide (5 mg, 10 mg, or 25 mg), both added on to metformin. The study included an extension phase of up to 204 weeks.
- Study 12 (N = 180): A 24-week placebo-controlled study with patients randomized (1:1) to either dapagliflozin 10 mg or placebo added on to metformin. The study included an extension phase of up to 78 weeks.
- Study 14 (N = 546): A 24-week placebo-controlled study with patients randomized (1:1:1:1) to either dapagliflozin 2.5 mg, dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo added on to metformin. The study included an extension phase of up to 78 weeks.
- Study 18 (N = 534): A 24-week study with patients randomized (1:1:1) to either dapagliflozin 10 mg, saxagliptin 5 mg, or dapagliflozin (10 mg per day) plus saxagliptin (5 mg per day) added on to metformin. This study was designed to compare triple therapy versus dual therapy; therefore, no analysis comparing dapagliflozin to saxagliptin was conducted.
- Study 5 (N = 438): Enrolled patients with inadequate glycemic control with a sulfonylurea. Patients were randomized (1:1:1) to either dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo added on to their existing sulfonylurea therapy. The study included an extension phase of up to 48 weeks.
- Study 6 (N = 598): A 24-week placebo-controlled study with patients randomized (1:1:1) to either dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo added on to insulin. The study included an extension phase of up to 80 weeks.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Glycemic control — change from baseline in A1C, proportion of patients with A1C less than 7% at end point, and change from baseline in fasting plasma glucose (FPG)
- Body weight — change from baseline in body weight
- Blood pressure — change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP)
- Hypoglycemia — events of hypoglycemia, including severe hypoglycemia
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

Change from baseline in A1C was the primary outcome in all studies, with the exception of Study 12, which evaluated change in total body weight as the primary end point.

Efficacy

Add-on to Metformin (Studies 4, 12, 14, and 18)

- In Study 4, dapagliflozin was non-inferior to glipizide in both the intention-to-treat (0.00%; 95% confidence interval [CI], −0.11 to 0.11) and per-protocol (0.00%; 95% CI, −0.12 to 0.12) analyses. There was no difference between dapagliflozin and glipizide in the proportion of patients achieving A1C of < 7% after 52 weeks (difference in proportions −4.6%; 95% CI, −10.9 to 1.7).
- There was a statistically significant reduction in A1C versus placebo after 24 weeks with dapagliflozin 5 mg and 10 mg in Studies 12 and 14:
  - Dapagliflozin 5 mg versus placebo: −0.41% (95% CI, −0.61 to −0.21)
  - Dapagliflozin 10 mg versus placebo: −0.54% (95% CI, −0.74 to −0.34) in Study 14 and −0.28% (95% CI, −0.42 to −0.15) in Study 12.
- There was no statistically significant difference in FPG between dapagliflozin and glipizide in Study 4. Both the 5 mg and 10 mg doses of dapagliflozin were superior to placebo for reducing FPG in Studies 12 and 14:
  - Dapagliflozin versus glipizide: 0.2 mmol/L (95% CI, −0.4 to 0.0) in Study 4
  - Dapagliflozin 5 mg versus placebo: −0.9 mmol/L (95% CI, −1.3 to −0.4) in Study 14
  - Dapagliflozin 10 mg versus placebo: −1.0 mmol/L (95% CI, −1.4 to −0.6) in Study 14 and −0.9 mmol/L (95% CI, −1.3 to −0.6) in Study 12.
- In all studies with background metformin, there was a statistically significant reduction in body weight in the dapagliflozin treatment groups compared with glipizide or placebo:
  - Dapagliflozin versus glipizide: –4.65 kg (95% CI, –5.14 to –4.17) in Study 4
  - Dapagliflozin 5 mg versus placebo: −2.16 kg (95% CI, −2.81 to −1.50) in Study 14
  - Dapagliflozin 10 mg versus placebo: −1.97 kg (95% CI, −2.63 to −1.31) in Study 14 and −2.08 kg (95% CI, −2.84 to −1.31).
- In Study 4, there was a statistically significant reduction in SBP (−5.0 mm Hg; 95% CI, −6.7 to −3.4) and DBP (−1.2 mm Hg; 95% CI, −2.3 to −0.2) in the dapagliflozin group compared with the glipizide group. In the placebo-controlled studies, statistical analysis for mean change in blood pressure was not reported in all studies; however, there was no significant difference in change in SBP or DBP between dapagliflozin 10 mg and placebo in Study 12.

Add-on to a Sulfonylurea (Study 5)

- Compared with placebo, there was a statistically significant reduction in A1C in both the dapagliflozin 5 mg (−0.49%; 95% CI, −0.67 to −0.32) and the dapagliflozin 10 mg groups (−0.68%; 95% CI, −0.86 to −0.51) after 24 weeks.
- Compared with placebo, there was a statistically significant reduction in SBP in both the dapagliflozin 5 mg (−2.8 mm Hg; 95% CI, −5.5 to −0.2) and 10 mg groups (−3.8 mm Hg; 95% CI, −6.4 to −1.2). There were no statistically significant differences between the dapagliflozin and placebo groups for DBP.
- There was a statistically significant reduction in body weight in the dapagliflozin treatment groups compared with placebo:
  - Dapagliflozin 5 mg versus placebo: −0.84 kg (95% CI, −1.47 to −0.21)
  - Dapagliflozin 10 mg versus placebo: −1.54 kg (95% CI, −2.17 to −0.92).

Add-on to Insulin (Study 6)

- In Study 6, there was a statistically significant reduction in A1C after 24 weeks in both the dapagliflozin 5 mg and dapagliflozin 10 mg groups compared with placebo.
  - Dapagliflozin 5 mg versus placebo: −0.52% (95% CI, −0.66 to −0.38)

  - Dapagliflozin 10 mg versus placebo: −0.60% (95% CI, −0.74 to −0.45).
- There was a statistically significant reduction in SBP compared with placebo in the dapagliflozin 10 mg group (−3.0; 95% CI, −5.5 to −0.4); however, the difference in the dapagliflozin 5 mg group was not statistically significant (−2.1; 95% CI, −4.6 to 0.4). There were no statistically significant differences between the dapagliflozin and placebo groups for DBP.

Harms (Safety and Tolerability)

Add-on to Metformin (Studies 4, 12, 14, and 18)

- In Study 4, a statistically significantly lower proportion of patients experienced at least one event of hypoglycemia after 52 weeks with dapagliflozin versus glipizide (adjusted mean difference −37%; 95% CI, −42% to −32%); $P < 0.0001$). The risk of hypoglycemia was similar between the dapagliflozin and placebo groups in the studies with metformin as a background therapy and slightly higher with dapagliflozin in the studies with a sulfonylurea or insulin as background therapy (Studies 5 and 6, respectively).
- There were numerically more genital infections with dapagliflozin than with glipizide (12% versus 3%) and numerically more urinary tract infections in females (14% versus 9%). Across the placebo-controlled studies, the proportion of patients with urogenital infections was consistently greater with dapagliflozin than with placebo.
- The proportions of patients who experienced at least one adverse event were:
  - Study 4: dapagliflozin (78%) and glipizide (78%)
  - Study 12: dapagliflozin 10 mg (43%) and placebo (40%)
  - Study 14: dapagliflozin 5 mg (69%), dapagliflozin 10 mg (73%), and placebo (64%)
  - Study 18: dapagliflozin (53%), saxagliptin (49%), and dapagliflozin plus saxagliptin (49%)
  - Study 5: dapagliflozin 5 mg (48%), dapagliflozin 10 mg (50%), and placebo (47%)
  - Study 6: dapagliflozin 5 mg (66%), dapagliflozin 10 mg (67%), and placebo (65%).
- The proportions of patients with at least one serious adverse event were:
  - Study 4: dapagliflozin (9%) and glipizide (11%)
  - Study 12: dapagliflozin 10 mg (7%) and placebo (1%)
  - Study 14: dapagliflozin 5 mg (3%), dapagliflozin 10 mg (3%), and placebo (4%)
  - Study 18: dapagliflozin (1%), saxagliptin (3%), and dapagliflozin plus saxagliptin (1%)
  - Study 5: dapagliflozin 5 mg (7%), dapagliflozin 10 mg (9%), and placebo (5%)
  - Study 6: dapagliflozin 5 mg (5%), dapagliflozin 10 mg (7%), and placebo (7%).
- In Study 4, the proportion of patients who withdrew due to an adverse event was slightly higher in the dapagliflozin group compared with the glipizide group in both the core phase (9% versus 6%) and in the extension phase (13% versus 11%). In the placebo-controlled trials, the proportion of patients who withdrew as a result of adverse events was generally similar between the dapagliflozin and placebo groups, with the exception of Study 12, in which a greater proportion of dapagliflozin-treated patients withdrew than placebo-treated patients.
- The proportions of patients who withdrew as a result of adverse events were:
  - Study 4: dapagliflozin (9%) and glipizide (6%)
  - Study 12: dapagliflozin 10 mg (4%) and placebo (0%)
  - Study 14: dapagliflozin 5 mg (2%), dapagliflozin 10 mg (3%), and placebo (4%)
  - Study 18: dapagliflozin (1%), saxagliptin (0%), and dapagliflozin plus saxagliptin (1%)
  - Study 5: dapagliflozin 5 mg (3%), dapagliflozin 10 mg (3%), and placebo (2%)
  - Study 6: dapagliflozin 5 mg (6%), dapagliflozin 10 mg (4%), and placebo (4%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing dapagliflozin to glyburide (a sulfonylurea) and linagliptin (a DPP-4 inhibitor) as add-on therapy to metformin, sulfonylurea, or insulin (with or without metformin). Efficacy data for the metformin plus dapagliflozin versus metformin plus sulfonylurea comparison were obtained from Study 4. Efficacy data for the other comparisons were obtained from three manufacturer-funded network meta-analyses (NMAs). The time horizon was the patient's lifetime (up to 40 years) using a Canadian public payer perspective. The economic analyses were carried out using the Cardiff Diabetes Model. Compared with metformin plus sulfonylurea, the manufacturer reported that metformin plus dapagliflozin resulted in an ICUR of $25,762 per QALY. For all the other comparisons (i.e., dapagliflozin compared with a DPP-4 inhibitor as add-on to metformin, a sulfonylurea, or insulin), dapagliflozin dominated the DPP-4 inhibitor (i.e., dapagliflozin resulted in more benefit at a lower cost than the DPP-4 inhibitor).

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

- The manufacturer's model applied a utility reduction of 0.0472 per 1 unit increase in body mass index (BMI), and a utility increase of 0.0171 for every unit decrease in BMI throughout the duration of the analysis, based on a manufacturer-funded Canadian utility elicitation study. Lower disutility values (0.0061 and 0.001950) have been reported in the literature.
- The price of linagliptin in the model was $2.55 per 5 mg tablet. CDR noted that the lowest public list price of a DPP-4 inhibitor is $2.25 per 5 mg tablet of linagliptin.
- The efficacy data for dapagliflozin that were used in the economic model were based on the NMAs that pooled the data for dapagliflozin 5 mg and 10 mg. Evidence from the extension phase of Studies 14, 5, and 6 suggests that the effect of dapagliflozin on A1C and body weight tends to be slightly lower for 5 mg compared with 10 mg daily.
- The three NMAs pooled data across drug classes regardless of dosage strength, frequency or mode of administration, which did not allow a comparison of the two doses of dapagliflozin, nor a comparison of dapagliflozin against other SGLT-2 inhibitors.
- The manufacturer's economic evaluation did not account for any treatment discontinuation related to moderate to severe renal impairment.
- In base case 3, metformin was not included as a comparator although the Health Canada product monograph does not specify that dapagliflozin is to be used only in patients intolerant to metformin.
- For patients using insulin, dapagliflozin was compared with a DPP-4 inhibitor. Although most DPP-4 inhibitors in Canada are indicated for use as add-on combination therapy with insulins, the use of DPP-4 inhibitors for this indication has not been reviewed by CDR or listed for reimbursement by many of the public drug plans. The validity of DPP-4 inhibitors as a comparator to dapagliflozin in this base-case analysis warrants consideration.

When accounting for variations in disutility values with weight change, CDR found that the ICUR for dapagliflozin compared with a sulfonylurea as add-on to metformin ranges from $25,939 to $342,374 per QALY. When variations in disutility values associated with change in body weight and reimbursement costs for DPP-4 inhibitors were considered, the ICUR for dapagliflozin when compared with a DPP-4 inhibitor was as follows: as add-on to metformin range from $12,453 to $1,021,404 per QALY; as add-on to a sulfonylurea ranged from $11,654 to $384,158 per QALY; and, as add-on to insulin ranged from $2,486 to $53,123 per QALY.

At the submitted price of [redacted], dapagliflozin ([redacted]) [redacted] than most DPP-4 inhibitors (ranging from $2.55 to $2.98 per day) [redacted] than linagliptin 5 mg ($2.25 per day in some drug plans), metformin ($0.18 per day), and sulfonylureas (up to $0.43 per day).

Other Discussion Points:
CDEC noted the following:

- The included studies were not designed to examine the effects of dapagliflozin on microvascular or macrovascular outcomes, and the relationship between A1C and vascular outcomes is uncertain.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- Direct or indirect comparisons assessing the comparative efficacy of dapagliflozin versus other antihyperglycemic drugs for the prevention of macrovascular and microvascular diabetes-related complications; such comparisons are needed.
- Direct or indirect comparisons between the addition of dapagliflozin to an existing insulin regimen and intensification of insulin treatment for patients inadequately controlled on their existing insulin regimen.

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.

October 21, 2015 Meeting
Regrets:

One CDEC member was unable to attend this portion of the meeting.

Conflicts of Interest:

None.

About This Document:
CDEC provides formulary listing 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 requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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