CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

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

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that dapagliflozin not be listed for the treatment of type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea.

Reason for the Recommendation:

- CDEC considered the single, placebo-controlled, randomized trial (RCT) conducted in patients with type 2 diabetes who had inadequate glycemic control with metformin and a sulfonylurea (study 5; N = 218) to have significant limitations. These included the small sample size given the high prevalence of type 2 diabetes, significant imbalances in baseline characteristics, and the absence of a 5 mg once per day dose in the dapagliflozin treatment group (i.e., the starting dose recommended by Health Canada).
- Due to these limitations, CDEC considered the estimated clinical benefit of treatment with dapagliflozin to be uncertain in this patient population.

Of Note
CDEC noted that there are several other alternative pharmacotherapies available for the treatment of type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea.

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

- Safety and efficacy of dapagliflozin 5 mg once per day in patients with inadequate glycemic control with metformin and a sulfonylurea.
- 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.
- Study population was overwhelmingly white, which limited the generalizability to the Canadian population.

Background:
Dapagliflozin is an SGLT-2 inhibitor indicated for use in patients with type 2 diabetes to improve glycemic control in combination with: metformin; a sulfonylurea; metformin and a sulfonylurea; or insulin (alone or with metformin), when the existing therapy, along with diet and exercise, does not provide adequate glycemic control. This CADTH Common Drug Review (CDR) submission is for the use of dapagliflozin in combination with metformin and a sulfonylurea.

Submission History:
Dapagliflozin in combination with metformin, a sulfonylurea, or insulin (alone or with metformin) was previously reviewed for use in patients with type 2 diabetes to improve glycemic control and received a recommendation to list with clinical criteria and conditions (see *CDEC Final Recommendation*, November 20, 2015).

Summary of CDEC Considerations
CDEC considered the following information prepared by CDR: a systematic review of RCTs and pivotal studies of dapagliflozin in combination with metformin and a sulfonylurea, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients living 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, imposes a psychological and emotional burden on many patients and caregivers.
- Many of the currently available therapies can cause significant weight gain (an especially undesirable side effect given that it is associated with increased disease severity and frustration for patients), hypoglycemia, and other adverse effects.

Clinical Trials
The CDR systematic review included one international, multicenter, manufacturer-sponsored, placebo-controlled, double-blind (DB) RCT. Study 5 (N = 218) had a 24-week DB period and a 28-week site- and subject-blinded extension period that evaluated the efficacy and safety of dapagliflozin 10 mg once daily in patients with type 2 diabetes who had inadequate glycemic control (7.0% ≤ HbA1c ≤ 10.5%) on a combination therapy of ≥ 1,500 mg/day metformin and ≥ 50% the maximum dose of a sulfonylurea. Patients were randomized in a 1:1 ratio to either dapagliflozin 10 mg or placebo (with a background of metformin and a sulfonylurea) after an 8-week single-blind, placebo lead-in period.

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

- Glycemic control — change from baseline in HbA1c, proportion of patients with HbA1c 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.

The primary outcome was the change from baseline in HbA1c at week 24. Results were presented with statistical adjustment to attempt to account for notable imbalances between treatment groups at baseline.

Efficacy

- There was a statistically significant reduction from baseline in HbA1c at week 24 in the dapagliflozin group compared to the placebo group (adjusted mean change versus placebo −0.69 [95% CI, −0.89 to −0.49]; $P < 0.0001$).
- The proportion of patients achieving an HbA1c <7% at week 24 was a key secondary endpoint in study 5, and was statistically significantly greater in the dapagliflozin group compared to the placebo group (33.3% versus 10.2%; adjusted mean difference versus placebo 20.7 [95% CI, 10.7 to 30.6]; $P < 0.0001$).
- There was a statistically significant greater reduction from baseline in body weight at week 24 in the dapagliflozin group compared to the placebo group (adjusted mean change versus placebo of −2.07 kg [95% CI, −2.79 to −1.35]; $P < 0.0001$).
- There was a statistically significantly greater reduction from baseline in SBP at week 8 in the dapagliflozin group compared to the placebo group (adjusted mean change versus placebo −3.76 mmHg [95% CI, −7.05 to −0.48]; $P = 0.0250$). This difference was maintained at week 24 (adjusted mean change versus placebo of −4.00 mmHg [95% CI, −7.14 to −0.87]; $P = 0.0125$), although this endpoint was not included in the testing hierarchy. The change from baseline in DBP at week 24 was statistically significantly greater in the dapagliflozin group compared to the placebo group (adjusted mean change versus placebo of −2.20 mmHg [95% CI, −3.99 to −0.42]; $P = 0.0158$), though this endpoint was not included in the testing hierarchy.

Harms (Safety and Tolerability)

- A total of 48.6% of patients in the dapagliflozin group and 51.4% of patients in the placebo group reported an adverse event during the 24-week DB period, with the most common adverse events with dapagliflozin being bronchitis, urinary tract infection, and pharyngitis.
- During the 24-week DB period, the proportion of patients reporting a serious adverse event was 0.9% in the dapagliflozin group and 5.5% in the placebo group.
- During the 24-week DB period, there was a greater proportion of patients in the dapagliflozin group who had a confirmed adverse event of hypoglycemia than in the placebo group (12.8% versus 2.8%). Most hypoglycemia episodes were minor, with a plasma glucose level between 3.0 and 3.5 mmol/L.
- During the 24-week DB period, genital infections were more common with dapagliflozin than placebo (5.5% versus 0%), urinary tract infections were balanced between groups (6.4%), renal impairment was reported in 2 patients (1.8%) in the dapagliflozin group, and bone fractures were reported in one patient (0.9%) in the placebo group.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing dapagliflozin to a dipeptidyl peptidase (DPP)-4 inhibitor (i.e., linagliptin) as add-on therapy to metformin and a sulfonylurea. Efficacy data were obtained from a manufacturer-sponsored network meta-analysis (NMA). A lifetime time horizon (up to 40 years) was used and the analysis was conducted from the Canadian public payer perspective using the Cardiff Diabetes Model. As add-on therapy to metformin and a sulfonylurea, the manufacturer reported that dapagliflozin dominated the DPP-4 inhibitor (i.e., dapagliflozin resulted in greater benefit at a lower cost than the DPP-4 inhibitor).

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

- 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 was applied throughout the duration of the analysis, based on a manufacturer-funded Canadian utility elicitation study. However, lower disutility values (0.0061 and 0.001950) for weight gain have been reported in the literature. Furthermore, there is uncertainty as to whether weight loss alone improves quality of life.
- The price for linagliptin in the model was $2.55 per 5 mg tablet; however, the lowest publicly-available list price for linagliptin is $2.25 per 5 mg tablet.
- The efficacy estimate for dapagliflozin used in the economic model was based on the submitted NMA, which included data only for dapagliflozin 10 mg. Although the manufacturer is requesting listing of both doses of dapagliflozin (5 mg and 10 mg daily) as add-on treatment to metformin and a sulfonylurea in patients with type 2 diabetes, no evidence was submitted to support the assumption that the efficacy of dapagliflozin 5 mg daily on HbA1c, weight loss, and SBP would be similar to that of dapagliflozin 10 mg daily.
- In the NMA submitted by the manufacturer, data were pooled across drug classes regardless of dose, frequency, or mode of administration.
- The analysis did not account for treatment discontinuation related to moderate to severe renal impairment.
- There is uncertainty regarding the long-term efficacy of compared treatments, which limits the validity of the long-term results predicted by the model.

When alternative utility values for weight change and the lower list price for linagliptin were applied, the incremental cost-utility ratio (ICUR) for dapagliflozin compared to a DPP-4 inhibitor as add-on to metformin and a sulfonylurea ranged from $8,259 to $71,360 per quality-adjusted life-year (QALY).

At the submitted price of $[redacted] per 5 mg or 10 mg tablet, dapagliflozin ($[redacted] daily) is less costly than most DPP-4 inhibitors (ranging from $2.55 to $2.98 daily) and GLP-1 agonists ($4.57 to $6.85 daily) but more expensive than linagliptin 5 mg ($2.25 daily in some drug plans).

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.

Regrets:
February 17, 2016: Three CDEC members were unable to attend the meeting.
April 20, 2016: None

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*.

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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