CDEC FINAL RECOMMENDATION

CANAGLIFLOZIN
(Invokana — Janssen Inc.)
Indication: Type 2 Diabetes Mellitus

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that canagliflozin be listed for the treatment of type 2 diabetes, if the following clinical criterion and condition are met:

Clinical Criterion
• Added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.

Condition
• Drug plan costs for canagliflozin should not exceed the drug plan cost of dipeptidyl peptidase-4 (DPP-4) inhibitors.

Reasons for the Recommendation:
1. Two randomized controlled trials (RCTs; DIA3015 and DIA3002) demonstrated that canagliflozin was superior to placebo and sitagliptin for improving glycemic control, reducing body weight, and lowering systolic blood pressure (SBP).
2. At the submitted price of $2.62 per 100 mg or 300 mg tablet, the CADTH Common Drug Review (CDR) estimated that the incremental cost-utility ratio (ICUR) for canagliflozin compared with sitagliptin ranges from being dominant (lower net cost and greater net quality-adjusted life-years [QALYs]) to $35,150 per QALY.

Background:
Canagliflozin is a sodium-glucose cotransporter-2 (SGLT-2) inhibitor indicated for patients with type 2 diabetes to improve glycemic control as monotherapy, in combination with metformin, with a sulfonylurea, with metformin and a sulfonylurea, with metformin and pioglitazone, or with insulin (with or without metformin), when these drugs do not provide adequate glycemic control. The current CDR submission for canagliflozin is for use in combination with metformin and a sulfonylurea in adult patients with type 2 diabetes mellitus to improve glycemic control when diet, exercise, and dual therapy do not provide adequate glycemic control.

Canagliflozin is available as 100 mg and 300 mg tablets and the recommended starting dose is 100 mg once daily. A dose of 300 mg once daily may be considered for patients who tolerated a...
100 mg once-daily dose and who need tighter glycemic control, provided they have an estimated glomerular filtration rate (eGFR) \geq 60 \text{ mL/min/1.73 m}^2, and who have a low risk of adverse reactions associated with reduced intravascular volume. Canagliflozin is contraindicated in patients with renal impairment with eGFR less than 45 \text{ mL/min/1.73 m}^2, patients with end-stage renal disease, or patients on dialysis.

**Summary of CDEC Considerations:**
CDEC considered the following information prepared by CDR: a systematic review of RCTs of canagliflozin 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 individuals living with type 2 diabetes.

**Patient Input Information**
The following is a summary of information provided by one patient group that responded to the CDR call for patient input:
- 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 and hypoglycemia.

**Clinical Trials**
The CDR review included two double-blind phase 3 RCTs investigating the efficacy and safety of canagliflozin in patients with type 2 diabetes and inadequate glycemic control with metformin and sulfonylurea combination therapy. DIA3015 (N = 756) randomized patients using metformin and a sulfonylurea to either canagliflozin 300 mg once daily or sitagliptin 100 mg once daily add-on therapy over a period of 52 weeks. DIA3002 (N = 469) randomized patients to either canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, or matching placebo added on to their existing metformin and sulfonylurea therapy over a period of 26 weeks in the primary study, and an additional 26 weeks in an extension study. Adults with type 2 diabetes were eligible for these studies if they had poor glycemic control (i.e., glycated hemoglobin [A1C] \geq 7\% and \leq 10.5\%) despite using the maximum tolerated dose of metformin (\geq 1,500 \text{ mg/day}) and a sulfonylurea (greater than or equal to half of the maximum recommended dose).

**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 and proportion of patients with a reduction in body weight of at least 5\%
- Blood pressure — change from baseline in SBP and diastolic blood pressure (DBP)
- Hypoglycemia — events of severe hypoglycemia and any hypoglycemia
- Serious adverse events, total adverse events, and withdrawals due to adverse events.
The primary efficacy end point in both studies was the difference in A1C levels from baseline to the end of the study period (52 weeks in DIA3015 and 26 weeks in DIA3002).

**Efficacy**

**Active-Controlled Trial (DIA3015)**

- Canagliflozin 300 mg once daily demonstrated both non-inferiority and superiority compared with sitagliptin 100 mg once daily for change from baseline in A1C in both the modified intention to treat (least squares mean difference [LSMD] –0.37%; 95% confidence interval [CI], –0.50% to –0.25%) and per-protocol data sets (LSMD –0.21%; 95% CI, –0.34% to –0.08%).
- A greater proportion of patients treated with canagliflozin 300 mg had an A1C value of less than 7% at week 52 compared with sitagliptin (47.6% versus 35.3%; odds ratio 1.80 [95% CI, 1.30 to 2.48]). However, the proportion of patients with an A1C of less than 6.5% was similar between the two groups (22.5% with canagliflozin and 18.9% with sitagliptin; odds ratio 1.27 [95% CI, 0.87 to 1.86]).
- There was a statistically significant difference favouring canagliflozin 300 mg over sitagliptin 100 mg for change from baseline in FPG (LSMD –1.34 [95% CI, –1.658 to –1.012], \(P < 0.001\)).
- The difference in percentage change in body weight between the canagliflozin 300 mg and sitagliptin 100 mg groups was statistically significant; –2.8% (95% CI, –3.3% to –2.2%). The proportion of patients whose body weight was reduced by at least 5% was 21% in the canagliflozin group compared with 6% in the sitagliptin group.
- There was a statistically significantly greater decrease from baseline in SBP observed in the canagliflozin 300 mg group compared with the sitagliptin 100 mg group (\(P < 0.001\)). The LSMD between the groups was –5.91 mmHg (95% CI, –7.64 mmHg to –4.18 mmHg). The difference in change from baseline in DBP also favoured canagliflozin compared with sitagliptin; –2.73 mmHg (95% CI, –3.81 mmHg to –1.66 mmHg).

**Placebo-Controlled Trial (DIA3002)**

- Compared with placebo, the LSMD in change from baseline in A1C was –0.71% (95% CI, –0.90 to –0.52%) for canagliflozin 100 mg once daily and –0.92% (95% CI, –1.11 to –0.73%) for canagliflozin 300 mg once daily. Results were similar in the per-protocol analysis; however, the effect sizes for canagliflozin compared with placebo were smaller (LSMD –0.54% [95% CI, –0.76% to –0.32%] for the 100 mg dose and –0.73% [95% CI, –0.96% to –0.51%] for the 300 mg dose).
- A statistically significantly greater proportion of patients had an A1C of less than 7% in the 100 mg canagliflozin group (43.2%) and 300 mg canagliflozin group (56.6%) compared with the placebo group (18.0%); odds ratio 4.42 (95% CI, 2.48 to 7.87) and 8.80 (95% CI, 4.86 to 15.95), respectively.
- Both doses of canagliflozin were statistically superior to placebo for change from baseline in FPG (\(P < 0.001\) for both). Compared with placebo, the LSMD was –1.24 (95% CI, –1.75 to –0.73) for 100 mg canagliflozin and –1.92 (95% CI, –2.43 to –1.41) for 300 mg canagliflozin.
- Compared with placebo, the difference in percentage change in body weight was –1.4% (95% CI, –2.1% to –0.7%) for 100 mg canagliflozin and –2.0% (95% CI, –2.7% to –1.3%) for 300 mg canagliflozin. A greater proportion of participants in the canagliflozin 300 mg (18%) and 100 mg (16%) groups achieved at least a 5% reduction in body weight compared with placebo (4%).
There was a greater LS mean decrease in systolic blood pressure from baseline in the canagliflozin 100 mg (−4.9 mmHg) and 300 mg (−4.3 mmHg) groups relative to the placebo group (−2.7 mmHg); however, the differences were not statistically significant (P = 0.077 and 0.201, respectively). Compared with placebo, differences in the change from baseline in DBP were −1.1 mmHg (95% CI, −2.7 mmHg to 0.4 mmHg) for 100 mg canagliflozin and −0.5 mmHg (95% CI, −2.1 mmHg to 1.0 mmHg) for 300 mg canagliflozin.

**Harms (Safety and Tolerability)**

- The proportion of patients who experienced at least one adverse event was reported as:
  - DIA3015: canagliflozin 300 mg (76.7%) and sitagliptin 100 mg (77.5%)
  - DIA3002: canagliflozin 100 mg (57.3%), canagliflozin 300 mg (62.2%), and placebo (63.5%).
- The proportion of patients with at least one serious adverse event was reported as:
  - DIA3015: canagliflozin 300 mg (6.4%) and sitagliptin 100 mg (5.6%)
  - DIA3002: canagliflozin 100 mg (3.2%), canagliflozin 300 mg (3.8%), and placebo (5.8%).
- The proportion of patients who withdrew as a result of adverse events was reported as:
  - DIA3015: canagliflozin 300 mg (5.3%) and sitagliptin 100 mg (2.9%)
  - DIA3002: canagliflozin 300 mg (5.8%), canagliflozin 100 mg (5.7%), and placebo (3.2%).
- The incidence of hypoglycemia was similar between the canagliflozin 300 mg (43.2%) and sitagliptin 100 mg (40.7%) groups in DIA3015. Hypoglycemia was more commonly reported in the canagliflozin groups (27.4% to 30.1%) than in the placebo group (15.4%) of DIA3002. Events classified as severe hypoglycemia were reported for 4.0% of patients in the canagliflozin group and 3.4% in the sitagliptin group. Severe hypoglycemia was rare in DIA3002, with just one event reported in the placebo and 100 mg canagliflozin groups and no events in the 300 mg group.
- In DIA3015, the incidences of vulvovaginal adverse events were higher in the canagliflozin 300 mg group compared with the sitagliptin group (15.3% versus 4.3%). In DIA3002, the incidences of vulvovaginal adverse events were higher in the two canagliflozin groups compared with the placebo group, with a higher incidence in the canagliflozin 300 mg group compared with the 100 mg group.
- There was a higher incidence of superficial genital infections in men in the canagliflozin 300 mg group compared with the sitagliptin 100 mg group (9.2% versus 0.5%). There was also a higher incidence of superficial genital infections in men treated with canagliflozin 100 mg (6.6%) and canagliflozin 300 mg (3.4%) compared with placebo (1.3%) in DIA3002.

**Cost and Cost-Effectiveness**
The manufacturer submitted a cost-utility analysis comparing canagliflozin 100 mg and 300 mg to sitagliptin 100 mg as a third-line drug added on to a combination of metformin and a sulfonylurea or metformin and pioglitazone. The effectiveness of canagliflozin 300 mg was compared with sitagliptin 100 mg using data from DIA3015. For the canagliflozin 100 mg and sitagliptin 100 mg comparison, a network meta-analysis (NMA) was used to populate the analyses in the absence of head-to-head trial data. The reference case time horizon was the patient’s lifetime (up to 40 years) using the Canadian public payer perspective. The economic analyses were carried out using the Economics and Health Outcomes Model of Type 2 Diabetes Mellitus (ECHO-T2DM). The disutility weights associated with complications of type 2 diabetes were primarily sourced from the CADTH Optimal Use Report for Third-Line Pharmacotherapy for Type 2 Diabetes and the literature. Unit costs for drugs were obtained from Quebec and Ontario formularies. Resource utilization associated with managing severe hypoglycemic...
episodes was derived from the same sources used in the CADTH Optimal Use Report for Third-Line Pharmacotherapy for Type 2 Diabetes. Costs associated with managing long-term diabetes-related complications were obtained from several published sources and expert opinion. The manufacturer reported that, when used adjunctively with metformin and a sulfonylurea or metformin and pioglitazone, canagliflozin 100 mg and 300 mg is dominant compared with sitagliptin 100 mg (less costly and associated with more QALYs).

CDR identified the following key limitations with the manufacturer’s pharmacoeconomic submission:

- Comparators did not include all available third-line treatments, such as insulin and glucagon-like peptide-1 (GLP-1) agonists, and did not account for variation in the pricing of DPP-4 inhibitors across the CDR-participating drug plans. CDR noted that the lowest public list price of a DPP-4 inhibitor is $2.25 per 5 mg tablet of linagliptin.
- In the absence of head-to-head trials comparing canagliflozin 100 mg and sitagliptin 100 mg, many clinical inputs (e.g., cholesterol, triglycerides, genital mycotic infections, and urinary tract infections) were taken from the intervention group of the trials for each individual comparator, thus creating an unadjusted indirect comparison.
- The manufacturer applied a disutility of 0.0061 per 1 kg/m² increase above a body mass index of 25 kg/m² for type 2 diabetes, based on Bagust and Beale (2005). A lower disutility value (0.001950) has been reported in the literature in the management of obesity.
- The model assumed a greater rate of hypoglycemic events with sitagliptin, which was not supported by the submitted NMA.

When accounting for these limitations, CDR reanalyses showed that the ICUR for canagliflozin (300 mg and 100 mg) compared with sitagliptin 100 mg ranges from being dominant to $35,150 per QALY.

At the submitted price of $2.62 per 100 mg or 300 mg tablet, canagliflozin ($2.62 per day) costs less than saxagliptin 5 mg ($2.84 per day) and sitagliptin 100 mg ($2.95 per day), but more than linagliptin 5 mg ($2.25 to $2.55 per day).

Other Discussion Points:
CDEC noted the following:

- CADTH’s Optimal Use Recommendations for Second- and Third-Line Therapy for Patients with Type 2 Diabetes, issued in 2013, indicate that neutral protamine Hagedorn (NPH) insulin is the preferred option for patients inadequately controlled on metformin plus a sulfonylurea. In circumstances where patients are unable to use insulin as a third-line option, CDEC recommended that a DPP-4 inhibitor be added to metformin and sulfonylurea therapy.
- DIA3002 and DIA3015 were not designed to examine the effects of canagliflozin 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 canagliflozin versus other antihyperglycemic drugs for the prevention of macrovascular and microvascular diabetes-related complications; such comparisons are needed.
- First Nations people were under-represented in the included trials.

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

December 10, 2014 Meeting

Regrets:
None

Conflicts of Interest:
The CDEC Chair recused herself and did not participate in the deliberations. The Vice-Chair acted as the Chair for this drug review.

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 not requested the removal of confidential information.

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