CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

CANAGLIFLOZIN AND METFORMIN HYDROCHLORIDE
(Invokamet — Janssen Inc.)
Indication: Type 2 Diabetes Mellitus

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that canagliflozin and metformin hydrochloride (canagliflozin/metformin) be reimbursed for patients with type 2 diabetes mellitus if the following criterion and condition are met:

Criteria
Patients who are already stabilized on therapy with metformin and canagliflozin, to replace the individual components of canagliflozin and metformin, for those patients who:

- Have inadequate glycemic control on metformin and a sulfonylurea, and for whom insulin is not an option.

Condition
Drug plan costs for the canagliflozin/metformin fixed-dose combination (FDC) should not exceed the combined cost of canagliflozin and metformin administered separately.

Reasons for the Recommendation:

1. In eight studies, canagliflozin/metformin FDC given twice daily has been shown to be bioequivalent to comparable doses of the individual drug components given twice daily in both fasting and fed conditions. This FDC product reduces the overall pill burden and regimen complexity for patients who would have taken these medications individually.
2. In study DIA2003, at 18 weeks, the canagliflozin/metformin FDC was shown to achieve a statistically higher reduction of glycated hemoglobin A1C compared with placebo and metformin. In addition, statistical significance was shown at 18 weeks for body weight, and the proportion of participants who achieved a hemoglobin A1C of < 7%.
3. At the submitted price, the canagliflozin/metformin FDC is more costly than the combination of the individual components. The annual incremental cost for the FDC is between $75 and $110.

Background:
Invokamet — an FDC of canagliflozin and metformin hydrochloride — is indicated to improve glycemic control as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus inadequately controlled on a sulfonylurea in combination with metformin or in patients already

being treated and achieving glycemic control with a sulfonylurea in combination with metformin and canagliflozin as separate tablets.

Canagliflozin/metformin FDC is available in the following six FDC regimens: 50 mg/500 mg, 50 mg/850 mg, 50 mg/1,000 mg, 150 mg/500 mg, 150 mg/850 mg, and 150 mg/1,000 mg.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the clinical evidence (bioequivalence, efficacy, and safety) for canagliflozin/metformin hydrochloride, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients.

The clinical efficacy and safety data for supporting the use of canagliflozin/metformin FDC to replace canagliflozin + metformin used concurrently in separate tablets was based on two pivotal phase 3 clinical studies for canagliflozin, which were the key evidence of a previous CDR review for canagliflozin as a third-line therapy added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea. In January 2015, canagliflozin received a CDEC recommendation for the treatment of type 2 diabetes as 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. Therefore, the two phase 3 studies mentioned above are not included as part of the present submission.

In addition to the two previously reviewed pivotal phase 3 clinical studies for canagliflozin, and the supplied pivotal bioequivalence trials for canagliflozin/metformin FDC, the manufacturer also submitted an 18-week supportive phase 2, placebo-controlled randomized control trial (RCT), DIA2003. Study DIA2003 assessed the efficacy and safety of canagliflozin (50 mg or 150 mg, twice daily) in type 2 diabetes mellitus patients who were inadequately controlled on metformin monotherapy.

Patient Input Information:
The following is a summary of information provided by two patient groups, Canadian Diabetes Association (CDA) and BC & Yukon Branch, Kidney Foundation of Canada (KFC), which responded to the CDR call for patient input. The CDA's submission was derived from a survey (March 2016) of 1,198 Canadians. Of these respondents, 988 were patients with type 2 diabetes and 61 respondents were caregivers. The KFC's submission was also based on a survey (January 2016) of 20 patients with diabetes and kidney disease.

- Many people with type 2 diabetes fail to achieve optimal glycemic control and are therefore at risk for both acute and chronic diabetes complications.
- Diabetes requires considerable self-management, including healthy eating, regular physical activity, healthy body weight, taking diabetes medications as prescribed, monitoring blood glucose, and managing stress. The majority of patients indicated that self-management of diabetes is very challenging, unrelenting, and overwhelming.
- Patients indicated that current therapies result in better blood glucose and A1C levels but lead to adverse events, such as low blood glucose, weight gain, or gastrointestinal (GI) adverse events.

- Patients mentioned that taking multiple medications not only reminds them that they have a life-threatening disease — diabetes — but is also challenging on busy days.

Clinical Trials

The primary source of safety data for canagliflozin/metformin FDC was based on two pivotal phase 3 clinical trials for canagliflozin previously reviewed by CDR (data not provided in this report, as mentioned above). For this review, the phase 2 study (DIA2003) provided additional data for canagliflozin/metformin FDC.

Outcomes

- 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
- 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.

Efficacy

The phase 2 study (DIA2003) provided additional efficacy data for canagliflozin/metformin FDC:

- A1C: In study DIA2003, at the end of 18 weeks, A1C decreased by 0.44% ($P < 0.001$) and 0.60% ($P < 0.001$) for patients treated with canagliflozin 50 mg and 150 mg twice daily, respectively, as compared with placebo. A greater proportion of patients achieved an A1C < 7.0% at week 18 when treated with canagliflozin 50 mg and 150 mg twice daily versus placebo (47.8% [$P < 0.05$], 57.1% [$P < 0.001$], and 31.5%, respectively).
- Body weight: Statistically significant reductions in body weight (as measured by least squares mean (LSM) per cent change from baseline) were observed with canagliflozin 50 mg and 150 mg twice daily compared with placebo at the end of 18 weeks (LSM difference [standard error (SE)]: –2.2% [–2.1] and –2.6% [–2.6], respectively; $P < 0.001$ for both dose regimens).
- Systolic blood pressure (SBP): Treatment with canagliflozin 50 mg or 150 mg (twice daily) was also associated with reductions in SBP compared with placebo (LSM difference [95% confidence interval (CI)] [mm Hg], –5.4 [–8.4 to –2.3] and –5.7 [–8.7 to –2.6], respectively).

Bioequivalence

Findings from six phase 1 studies indicated that all six strengths of canagliflozin/metformin FDC appear to be bioequivalent to its individual components given concurrently in separate tablets. Results from studies DIA1070 and DIA1071 demonstrated [redacted] between the metformin component in canagliflozin/metformin FDC tablets and the Canadian formulation of metformin IR in fed and fasted healthy participants. The predefined criteria to establish bioequivalence were met in all eight studies; namely, the 90% CI of the geometric mean ratio of AUC_{last} (or $AUC_{0\text{-}t}$) and C_{max} of the test to reference product was within the bioequivalence limits of 80% to 125%. Furthermore, the bioequivalence of canagliflozin/metformin FDC was validated in two more studies (studies DIA1032 and DIA1037) that demonstrated that the bioequivalence of canagliflozin dosed at 100 mg or 300 mg a day in either a twice-daily or once-daily format

was comparable and the bioequivalence of canagliflozin/metformin FDC was not affected by the administration of high-fat meal.

Harms (Safety and Tolerability)

For this review, the phase 2 study (DIA2003) provided additional safety data for canagliflozin/metformin FDC. Overall, study DIA2003 did not raise any new signals that were not reported by previous clinical studies reviewed by CDR for canagliflozin. The canagliflozin/metformin FDC regimens appear to have similar tolerability and safety profiles to the individually coadministered components. Furthermore, study DIA1032 found that canagliflozin was well tolerated in both once-daily and twice-daily treatment arms (either 100 mg or 300 mg total daily doses) with no meaningful differences between either dosing regimens or total daily doses; study DIA1037 reported that canagliflozin/metformin FDC 150 mg/1,000 mg was generally well tolerated in both a fed and fasted state. However, because study DIA1032 and study DIA1037 were conducted in healthy volunteers, whether the findings of the safety outcomes in the two above studies can be generalizable to type 2 diabetes mellitus patients is unknown.

Cost and Cost-Effectiveness

The manufacturer submitted an analysis comparing the drug costs of canagliflozin/metformin FDC (50 mg/500 mg, 50 mg/850 mg, 50 mg/1,000 mg, 150 mg/500 mg, 150 mg/850 mg, or 150 mg/1,000 mg twice daily) to the individual components, canagliflozin and metformin. At the submitted price of $1.5338 per tablet regardless of strength ($3.07 per day), the annual cost of canagliflozin/metformin FDC ($1,120 per patient) was $99 to $132 higher than equivalent dose combinations of the individual components at list prices ($988 to $1,020 per patient), excluding markups and dispensing fees. When an 8% markup and $8.83 dispensing fee were applied, canagliflozin/metformin FDC cost $75 to $110 per patient per year more than the separate components. The daily cost of canagliflozin/metformin FDC was also higher than the daily cost of dapagliflozin/metformin FDC ($2.62, based on the current wholesale list price), which has the same list price as dapagliflozin alone.

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.

July 20, 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 requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

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