CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

EMPAGLIFLOZIN / METFORMIN HYDROCHLORIDE (Synjardy — Boehringer Ingelheim Canada Ltd.) Indication: Type 2 Diabetes Mellitus

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

Clinical Criterion:
- Patients who are eligible to receive metformin and empagliflozin based on participating drug plan reimbursement criteria, to replace the individual components of empagliflozin and metformin.

Condition:
- Drug plan costs for the empagliflozin/metformin FDC should not exceed the combined cost of empagliflozin and metformin administered separately.

Reasons for the Recommendation:
1. Three randomized controlled trials (RCTs) (Study 1245.23$_{met}$ [N = 638], Study 1245.23$_{met+su}$ [N = 669], and Study 1245.19 [N = 499]) demonstrated that empagliflozin and metformin administered separately twice daily is statistically significantly superior to placebo in reducing glycated hemoglobin (A1C) after 24 weeks of treatment among patients on background therapy of metformin alone, metformin and sulfonylurea, and metformin and pioglitazone.
2. Empagliflozin/metformin FDC has been shown to be bioequivalent to similar doses of the individual drug components given twice daily. This FDC product likely reduces the overall pill burden and regimen complexity for patients who would have taken these medications individually.
3. At the submitted price ($1.35 per tablet, or $2.70 per day, for all six strengths), the empagliflozin/metformin FDC is $2 to $35 less expensive than the combination of the individual components, or $35 to $70 less expensive if pharmacy fees and markup are included.

Background:
Synjardy is an FDC of empagliflozin and metformin hydrochloride. It has a Health Canada–approved indication as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus who are inadequately controlled on:

- Metformin
- Sulfonylurea in combination with metformin
- Pioglitazone in combination with metformin
- Insulin in combination with metformin

Or in patients already being treated and achieving glycemic control with:

- Metformin and empagliflozin as separate tablets
- Sulfonylurea in combination with metformin and empagliflozin as separate tablets
- Pioglitazone in combination with metformin and empagliflozin as separate tablets
- Insulin in combination with metformin and empagliflozin as separate tablets.

Synjardy is available as 5 mg/500 mg, 5 mg/850 mg, 5 mg/1,000 mg, 12.5 mg/500 mg, 12.5 mg/850 mg, 12.5 mg/1,000 mg (empagliflozin/metformin hydrochloride) oral tablets. The product monograph recommends twice-daily dosing.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of empagliflozin administered in combination with metformin, a review of manufacturer-provided information on bioequivalence, 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 three surveys. CDEC heard the following:

- 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.
- Patients also indicated that current treatments can require a large number of pills and/or injections. Hence, FDC products, such as empagliflozin/metformin, may help reduce pill burden, which may promote greater adherence and improved quality of life.

Clinical Trials

The CDR review included three manufacturer-submitted pivotal studies. They were double-blind, placebo-controlled, multi-centre RCTs. All three studies had a 24-week treatment period that evaluated the efficacy and safety of empagliflozin 10 mg or 25 mg once daily in patients with type 2 diabetes who had inadequate glycemic control (A1C ≥ 7.0% and ≤ 10%) on a background therapy of metformin alone (Study 1245.23$_{met}$), metformin + sulfonylurea (Study 1245.23$_{met+su}$), or metformin and pioglitazone (Study 1245.19). No phase 3 RCTs of empagliflozin/metformin FDC were identified from the literature search.

Additional evidence was summarized in the appendices of the CDR Clinical Review report, including evidence from two non-pivotal, double-blind, phase 3 RCTs: Study 1245.28 (N = 1,549; 104 weeks) compared empagliflozin 25 mg once daily against glimepiride (1 mg to 4 mg daily) for patients with inadequate glycemic control with metformin monotherapy, and Study 1245.49 (N = 566; 52 weeks) compared the addition of empagliflozin (10 mg or 25 mg once

daily) against placebo for patients with inadequate glycemic control on their existing multiple daily insulin with or without metformin. As well, CDR reviewed evidence from four phase 1, single-dose, open-label crossover RCTs (Studies 1276.5, 1276.6, 1276.7, and 1276.8) that evaluated the bioequivalence of empagliflozin and metformin administered as an FDC tablet compared with administration of the individual components. Lastly, key findings of the 1245.31 extension study and a phase 2b, double-blind RCT (Study 1275.10) conducted to evaluate the efficacy and safety of empagliflozin twice daily versus once daily were reviewed.

Outcomes

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

- Mortality
- Glycemic control — change from baseline in A1C 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)
- Safety — serious adverse events, total adverse events, and withdrawals due to adverse events; events of hypoglycemia, including severe hypoglycemia.

The primary outcome in the three pivotal RCTs was the change from baseline in A1C at week 24.

Efficacy

- Three patients in the empagliflozin 10 mg or 25 mg groups and one patient in the placebo group died during the 24-week treatment period. The deaths were not considered to be related to the study drugs.
- Statistically and clinically significant greater reduction in A1C compared with placebo after 24 weeks was observed in the empagliflozin 10 mg or 25 mg groups in all three trials: The between-group differences in change in A1C from baseline ranged from –0.48% to –0.61%, –0.57% to –0.64%, and –0.59% to –0.64% for empagliflozin versus placebo when added on to metformin and pioglitazone, metformin alone, or metformin and sulfonylurea, respectively; all $P < 0.0001$. Empagliflozin as add-on therapy to the background therapy was also associated with a statistically and clinically significant greater reduction in FPG: The between-group differences in change in FPG from baseline ranged from –1.58 to –1.30 mmol/L, –1.59 to –1.47 mmol/L, and –1.60 mmol/L for empagliflozin versus placebo when added on to metformin and pioglitazone, metformin alone, or metformin and sulfonylurea, respectively; all $P < 0.0001$.
- Empagliflozin 10 mg or 25 mg was associated with a statistically significant greater weight loss in the study population after 24 weeks of treatment in all three studies: The magnitude of the reduction in body weight ranged from 1.63 kg to 2.16 kg versus placebo; all $P < 0.0001$.
- Empagliflozin 10 mg or 25 mg was superior to placebo in reducing SBP at 24 weeks in all three studies. The magnitude of the reduction in SBP versus placebo ranged from 2.1 mm Hg to 4.8 mm Hg (all $P < 0.05$); these values were not considered clinically significant. Empagliflozin was also superior to placebo in reducing DBP at 24 weeks when added on to metformin and pioglitazone and metformin alone ($P < 0.05$), but not when added on to metformin and sulfonylurea. None of the improvements in DBP were considered clinically significant.

- In the non-pivotal Study 1245.28, empagliflozin 25 mg was noninferior and superior to glimepiride for improving A1C (mean difference −0.11; 95% confidence interval [CI], −0.19 to −0.02) at 104 weeks. Empagliflozin was also statistically superior to glimepiride for reducing FPG (−0.69 mmol/L), SBP (−5.6 mm Hg), DBP (−2.7 mm Hg), and body weight (−4.46 kg) (all $P < 0.0001$).
- The bioequivalence of Synjardy to empagliflozin and metformin co-administered as individual tablets was demonstrated in healthy individuals.

Harms (Safety and Tolerability)

- Across the studies, the proportion of patients reporting an adverse event was balanced between the empagliflozin and the placebo groups: 57.1% to 67.9% for empagliflozin 10 mg once daily, 49.5% to 71.4% for empagliflozin 25 mg once daily, and 58.7% to 72.7% for placebo. Isolated cases of serious adverse events and withdrawal due to adverse events were reported across the studies and treatment groups.
- A higher proportion of patients in the empagliflozin group had a confirmed adverse event of hypoglycemia than in the placebo group at 24 weeks.
- More patients in the empagliflozin groups were reported to have developed a genital infection during the 24-week period than in the placebo group.
- The overall frequency of adverse events was generally similar across the treatment groups at week 76. The frequency and severity of the adverse events during the extension phase were similar to those reported during the core studies.

Cost and Cost-Effectiveness

The manufacturer submitted the market price of $1.3500 per tablet of empagliflozin/metformin for all strengths, or $2.70 per day.

An analysis comparing the annual cost of empagliflozin/metformin FDC to the costs of equivalent free-dose combinations of its individual components, other sodium-glucose cotransporter-2 (SGLT2) inhibitor/metformin combinations, and dipeptidyl-peptidase 4 (DPP-4) inhibitor/metformin combinations was provided by the manufacturer. The perspective was that of a Canadian public drug payer, and Ontario Drug Benefit list prices were used to estimate the cost of comparators.

The annual cost of empagliflozin/metformin FDC, including an 8% markup and an $8.83 dispensing fee every 30 days, was $1,172 per patient, which was $110 to $145 less expensive than free-dose combinations of empagliflozin and metformin. Empagliflozin/metformin FDC was also less expensive than other free-dose combinations of an SGLT2 or DPP-4 inhibitor and metformin, but more expensive than dapagliflozin/metformin FDC, saxagliptin/metformin FDC, and linagliptin/metformin FDC.

Key limitations in the analysis included an inappropriately averaged cost for each comparator, missing dose options, an overestimation of pharmacy fee savings, and the lack of head-to-head trials comparing empagliflozin to other SGLT2 or DPP-4 inhibitors.

According to CDR's reanalysis, when dispensing fees and markup were excluded, the annual cost of empagliflozin/metformin FDC ($986 per patient) was $2 to $35 (0% to 3%) per patient less than that of the corresponding free-dose combinations ($988 to $1,020 per patient). Use of empagliflozin/metformin FDC rather than the free-dose combination would also save one dispensing fee per claim. Empagliflozin/metformin FDC was less expensive than

canagliflozin/metformin FDC, free-dose combinations of dapagliflozin or canagliflozin plus metformin, sitagliptin/metformin FDC and alogliptin/metformin FDC, and all DPP-4 inhibitor plus metformin free-dose combinations with the exception of 5 mg linagliptin plus 1,000 mg metformin daily. However, empagliflozin/metformin FDC was 3%, 6%, and 1% more expensive than dapagliflozin/metformin FDC, saxagliptin/metformin FDC, and linagliptin/metformin FDC, respectively.

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.

September 21, 2016 Meeting:

Regrets:
Four members were absent.

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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