CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

Ertugliflozin/Metformin (Segluromet — Merck Canada Inc.)
Indication: Diabetes mellitus, type 2

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that ertugliflozin/metformin fixed-dose combination should not be reimbursed as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus to improve glycemic control.

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CADTH

ERTUGLIFLOZIN/METFORMIN (SEGLUROMET — MERCK CANADA INC.)

Indication: Diabetes mellitus, type 2

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ertugliflozin/metformin (ERT/MET) fixed-dose combination (FDC) not be reimbursed as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus to improve glycemic control.

Reasons for the Recommendation

1. Although evidence from two double-blind randomized controlled trials (RCTs) demonstrated that ERT (as add-on combination with metformin, or with metformin plus sitagliptin) statistically significantly improved glycated hemoglobin (A1C) after 26 weeks of treatment compared with placebo, ERT has not been demonstrated to have benefits on longer-term clinical outcomes such as reducing major cardiovascular events, which has been reported for some other sodium-glucose cotransporter-2 (SGLT2) inhibitors. Because there is no evidence of a cardiovascular benefit for ERT, if patients without a high risk of cardiovascular events were to initiate therapy with ERT/MET, those that subsequently experienced an increase in the risk of a cardiovascular event would need to be switched to an alternative treatment for which there is evidence of cardiovascular benefit. CDEC considered such a treatment strategy to be both difficult to implement and to be associated with an increased risk of harm to patients.
2. There are limited data to compare ERT/MET with other anti-hyperglycemic FDCs available for the treatment of adult patients with type 2 diabetes mellitus. One RCT (SU study) suggested that ERT, as add-on to metformin, was noninferior to glimepiride plus metformin for the change from baseline in A1C after 52 weeks, but for the ERT 15 mg once daily dosage form only. In another RCT (FACTORIAL), statistically significant short-term (26 weeks) improvements in A1C, body weight, and systolic blood pressure were observed for ERT plus sitagliptin, as add-on therapy to metformin, versus sitagliptin plus metformin. A manufacturer-submitted indirect treatment comparison of ERT versus other SGLT2 inhibitors and placebo suggested that ERT in combination with metformin for the treatment of type 2 diabetes mellitus is likely more efficacious than placebo; however, concrete conclusions could not be drawn with respect to the comparative efficacy with other SGLT2 inhibitors added onto metformin, or the relative safety of ERT/MET. Therefore, there is uncertainty regarding the long-term comparative benefits and safety of ERT/MET versus other treatments that are available for patients with type 2 diabetes mellitus, and there is no evidence that ERT/MET fulfills an unmet need in the treatment of patients with type 2 diabetes mellitus.

Discussion Points

- CDEC discussed the uncertainty in the clinical benefits of ERT/MET FDC relative to other SGLT2 inhibitor/metformin FDCs. Specifically, it was discussed that certain other SGLT2 inhibitors have a Health Canada-approved indication to reduce the incidence of cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease who have inadequate glycemic control. There is, as yet, no evidence that ERT (alone or combined with metformin)has cardiovascular benefits in patients with type 2 diabetes mellitus. The effects of ERT on cardiovascular outcomes are being studied in the VERTIS CV Study, which is ongoing and expected to be completed later in 2019.
- All patients with type 2 diabetes have significantly increased risk of cardiovascular diseases compared to the non-diabetic population. Most patients with type 2 diabetes therefore need both glycemic control to reduce the risk of microvascular complications as well as cardiovacsular risk reduction strategies. There are other antihyperglycemic drugs available that achieve both of these goals.

Background

Ertugliflozin and metformin FDC has a Health Canada indication for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are: inadequately controlled on metformin or already on metformin and ERT as individual components. It is also approved for use in combination with sitagliptin, 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 and sitagliptin, or already on metformin, sitagliptin, and ERT as individual components.

ERT is an SGLT2 inhibitor and metformin hydrochloride is a member of the biguanide class. ERT/MET FDC tablets are available as 2.5 mg ERT combined with 500 mg or 1,000 mg of metformin, and as 7.5 mg ERT combined with 500 mg or 1,000 mg of metformin. The Health Canada–recommended dose is one tablet twice daily.

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the clinical evidence (efficacy, safety, and bioequivalence) of ERT (in combination with metformin, or metformin plus sitagliptin), and a critique of the manufacturer's indirect treatment comparison and pharmacoeconomic evaluation. CDEC also considered input from a clinical expert with experience in treating patients with diabetes and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, Diabetes Canada, provided input for this submission. Patient perspectives were obtained from online surveys. The following is a summary of key input from the perspective of the patient group:

- Patients require considerable self-management, including in the areas of diet, physical activity, body weight, blood glucose, and stress, in addition to diabetic medications.
- Inadequate control of blood glucose can lead to a range of serious comorbidities such as cardiovascular diseases, blindness, kidney diseases, peripheral nerve damage, and erectile dysfunction.
- Survey respondents emphasized that dietary requirements, lifestyle modification, management of medications, and side effects (weight gain) are associated with a negative impact on patients' work, travel, and social life as well as increased stress, anxiety, and financial burden.
- The majority of participants responded that normalizing glucose levels as well as preventing hypoglycemia, change in weight, heart problems, and high blood pressure was important. Medications that are less costly, easy to administer, and avoid injections while minimizing side effects were the preferred choice of treatments.
- Also important was avoiding the requirement for multiple antidiabetic therapies and avoiding diabetes-associated complications.

Clinical Trials

The CDR clinical assessment of ERT included four double-blind RCTs of patients with type 2 diabetes mellitus (N = 463 to 1,326 per study). These trials evaluated the safety and efficacy of ERT 5 mg daily and ERT 15 mg daily (in combination with metformin, or metformin plus sitagliptin), compared with placebo or active comparators, in adults with type 2 diabetes and inadequate glycemic control. Three trials were 26 weeks in duration (MET, SITA2, FACTORIAL), and one active-controlled, noninferiority trial was 52 weeks in duration (SU study).

The available evidence on the efficacy of ERT was limited by the relatively short duration of the four trials (26 to 52 weeks) for a chronic condition, and the examination of surrogate outcomes (A1C, weight, and blood pressure). In these trials, the effects of ERT treatment may be overestimated due to the differential frequency of rescue and early discontinuation in the placebo and ERT groups. The single head-to-head study compared ERT with glimepiride, a sulfonylurea. There was no direct evidence comparing ERT with other diabetes drugs commonly used in Canada. Although the FACTORIAL study included ERT and sitagliptin control groups, the trial was not designed to test for differences between these drugs, and no between-group statistical comparison were reported.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol for ERT (Steglatro). Of these, CDEC discussed the following:

- glycemic control (i.e., change from baseline in A1C, proportion of patients with A1C < 7%)
- body weight
- blood pressure
- health-related quality of life based on the EuroQol 5-Dimensions questionnaire (EQ-5D)

- adverse events, serious adverse events, withdrawals due to adverse events, notable harms (hypoglycemia, genital and urinary tract infections)

The primary outcome in all trials was the change from baseline in A1C.

Efficacy

ERT as add-on therapy to metformin, or in combination with metformin and sitagliptin, was associated with statistically significant reductions in A1C (%) after 26 weeks compared with placebo (least squares [LS] mean difference −0.7% to −0.9%). ERT plus sitagliptin (as add-on to metformin) also showed statistically significant differences in A1C compared with ERT or sitagliptin (plus metformin) (LS mean difference −0.4% to −0.5%). More patients on ERT achieved glycemic targets (A1C < 7%) and fewer required rescue therapy than placebo. In the head-to-head study, ERT 15 mg daily as add-on therapy to metformin was noninferior to glimepiride for the change from baseline in A1C based on a 0.3% noninferiority margin (LS mean difference 0.1%; 95% confidence interval [CI], −0.02% to 0.22%). Noninferiority was not met for ERT 5 mg versus glimepiride, as the upper bound of the 95% CI for the difference between groups was not below 0.3%.

Input from patient groups reported weight loss and lowered blood pressure as important outcomes; however, it is unclear what degree of change may be considered clinically significant. The mean differences in the change from baseline in body weight ranged from −1.6 kg to −2.0 kg for ERT versus placebo and from −1.9 kg to −2.3 kg for ERT plus sitagliptin versus sitagliptin after 26 weeks of therapy, which were statistically significant. Somewhat larger mean differences were noted between ERT and glimepiride (−3.9 kg to −4.3 kg) at week 52, which was not unexpected, as the sulfonylureas are associated with weight gain. The mean differences in systolic blood pressure (SBP) between ERT and comparator groups in the MET, FACTORIAL, and SITA2 studies ranged from −2.8 mm Hg to −4.5 mm Hg, which the clinical expert consulted for this review considered clinically relevant. SBP data from the SU study was inconclusive due to the failure of a previous outcome in the statistical testing procedure. The differences between ERT and control groups for the change from baseline in diastolic blood pressure (DBP) were either not statistically significant or inconclusive in three of the four studies (SU, FACTORIAL, and SITA2). Although any reduction in weight or blood pressure may be viewed as positive by patients, it is not known if these changes translate into longer-term health benefits.

No statistically significant differences were detected between ERT and placebo for changes in health-related quality of life based on the EQ-5D instrument in the SITA2 study.

Harms (Safety)

- The overall frequency of adverse events was generally similar between groups within studies, and the proportion of patients who stopped using the study drug due to adverse events was low (≤ 5% per group).
- Serious adverse events were reported by 3% to 4% of patients who received placebo, 1% to 6% of those who received ERT (alone or with sitagliptin), and 1% to 3% of those who received sitagliptin or glimepiride. Genital mycotic infections were reported more frequently among patients who received ERT than other therapies.
- The frequency of documented or symptomatic hypoglycemia was highest in the glimepiride group (19% to 27%) compared with 1% to 9% of those who received ERT, and 2% to 4% of those who received placebo. Symptomatic hypoglycemia was included in the ordered statistical testing procedure for the SU trial, and the absolute difference between the ERT 15 mg and glimepiride groups was statistically significant (−14%; 95% CI, −18% to −10% [$P < 0.001$]). Data for the ERT 5 mg group was inconclusive due to the failure of a prior outcome in the statistical testing hierarchy.
- Although no new safety signals were identified in the extension studies, the included trials were of insufficient duration and sample size to capture rare events such as low trauma fractures, lower-limb amputations, or Fournier's gangrene that have been identified as possible risks with the SGLT2 inhibitors. Additional longer-term safety data will be available once the ongoing cardiovascular safety trial (VERTIS CV) is published.

Bioequivalence

None of the pivotal trials were conducted using the ERT/MET FDC. The manufacturer provided bioequivalence data for the combination product that suggested the pharmacokinetics of the combination are similar to those of the individual components. Bioequivalence between ERT/MET FDC and co-administration of corresponding doses of ERT and metformin tablets is reported in the product monograph for ERT/MET FDC.

Indirect Treatment Comparisons

The manufacturer submitted an indirect treatment comparison that compared ERT, as add-on therapy with metformin, to the three SGLT2 inhibitors approved in Canada (canagliflozin, dapagliflozin, and empagliflozin). The inclusion criteria for this focused review were limited to English-language RCTs that were 24 to 26 weeks in duration of adults with type 2 diabetes with an A1C level higher than 7% who received an SGLT2 inhibitor. The results of the Bayesian network meta-analysis (NMA) suggest that ERT has similar effects on A1C, weight, and blood pressure as other SGLT2 inhibitors in the short term. Although the NMA planned to examine hypoglycemia, urinary tract infections, genital infections, and overall adverse events, some of the models did not converge due to the low frequency of events. Thus, limited data were available on adverse effects. While the methods used to conduct the analyses seem to be adequate, the limited scope of the review meant that not all potentially relevant literature was used to inform the network. It is impossible to know what impact this may have had on the results, but the smaller sample size may have increased the chances of finding no difference between drugs. Based on the results of the submitted indirect treatment comparison, ERT in combination with metformin for the treatment of type 2 diabetes is likely more efficacious than placebo. Little can be elucidated on its comparative efficacy with other SGLT2 inhibitors or the relative safety of the product. Other than the SU study, direct evidence of the comparative efficacy of ERT with other diabetes treatments is lacking.

Cost and Cost-Effectiveness

The submitted price of ERT/MET FDC is $1.23 per tablet, regardless of strength (2.5 mg/500 mg, 2.5 mg/1,000 mg, 7.5 mg/500 mg, and 7.5 mg/1,000 mg). At the recommended dose of two tablets daily, the cost is $2.45 per day. The manufacturer presented two cost comparisons: one that compared the cost of ERT/MET FDC with SGLT2 in combination with metformin as individual products or FDCs, and the second that compared ERT/MET FDC with the individual components. In the first comparison, the manufacturer reported cost savings of up to $0.68 per day compared with SGLT2/metformin FDCs, and $0.38 to $2.90 per day compared with other individual SGLT2 and metformin components. In the second comparison, the manufacturer reported cost savings of $0.09 to $2.44 per day.

CADTH identified the following limitations and considerations with the manufacturer's submission:

- Drawing definitive conclusions on comparative costs is challenging given the uncertainty with the comparative efficacy of ERT/MET FDC and the lack of data comparing the dosing of the individual components of ERT and metformin as well as other antidiabetic drugs.
- Other publicly available prices were identified for metformin, which reduced the cost savings to $0.05 to $0.10 per day when comparing ERT/MET FDC with ERT and metformin as individual components.
- The use of ERT/MET FDC may lead to savings on dispensing fees per claim compared with its individual components.
- CADTH reviewers noted that other non-SGLT2 treatments in combination with metformin may be less costly than ERT/MET FDC.

September 19, 2018 Meeting

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

Two CDEC members did not attend.

Conflicts of Interest

None.

January 16, 2019 Meeting (Reconsideration)

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets

None.

Conflicts of Interest

None.