CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

ERTUGLIFLOZIN (STEGLATRO — MERCK CANADA INC.)
Indication: Diabetes mellitus, type 2

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that ertugliflozin should not be reimbursed as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus to improve glycemic control in those for whom metformin is inappropriate due to contraindications or intolerance (monotherapy), or as add-on combination treatment when metformin alone, or metformin plus sitagliptin do not provide adequate glycemic control.

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ERTUGLIFLOZIN (STEGLATRO — MERCK CANADA INC.)

Indication: Diabetes mellitus, type 2

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ertugliflozin (ERT) should not be reimbursed as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus to improve glycemic control in those for whom metformin is inappropriate due to contraindications or intolerance (monotherapy), or as add-on combination treatment when metformin alone, or metformin plus sitagliptin do not provide adequate glycemic control.

Reasons for the Recommendation

1. Although evidence from three double-blind randomized controlled trials (RCTs) demonstrated that ERT (as monotherapy, or as add-on combination with metformin, or with metformin plus sitagliptin) statistically significantly improved glycated hemoglobin (A1C) after 26 weeks of treatment versus 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, 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 with other antihyperglycemic drugs available for the treatment of adult patients with type 2 diabetes mellitus. One RCT (VERTIS SU) 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 only at 15 mg once-daily dosage. In another RCT (VERTIS FACTORIAL), statistically significant short-term (26 week) improvements were reported in A1C, body weight, and systolic blood pressure for ertugliflozin 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 as monotherapy or in combination with metformin is likely more efficacious than placebo; however, concrete conclusions could not be drawn with respect to the comparative efficacy or relative safety of ERT when compared with other SGLT2 inhibitors. Therefore, there is uncertainty regarding the long-term comparative benefits and safety of ERT versus other treatments that are available for patients with type 2 diabetes mellitus, and there is no evidence that ERT 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 relative to other SGLT2 inhibitors. 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 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 cardiovascular risk reduction strategies. There are other antihyperglycemic drugs available that achieve both of these goals.

Background

Ertugliflozin (ERT) has a Health Canada indication for use as monotherapy as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus for whom metformin is inappropriate due to contraindications or intolerance. It is also approved in combination with metformin, or metformin and sitagliptin, when these therapies, along with diet and exercise, do not provide adequate glycemic control.

ERT is an SGLT2 inhibitor. It is available as a 5 mg and 15 mg tablet and the Health Canada–approved dose is 5 mg or 15 mg daily.

Summary of Evidence Considered by CDEC Considerations

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of ERT and a critique of the manufacturer's indirect treatment comparison and pharmacoeconomic evaluation. CDEC also considered input from a clinical expert(s) 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 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 impaired work, travel and social life, 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 diabetes-associated complications.

Clinical Trials

The systematic review included five double-blind RCTs of patients with type 2 diabetes mellitus (N = 461 to 1,326 per study). These trials evaluated the safety and efficacy of ERT 5 mg daily and ERT 15 mg daily (alone or in combination with metformin, or metformin plus sitagliptin), compared with placebo or active comparators, in adults with type 2 diabetes and inadequate glycemic control. Four trials were 26 weeks in duration (VERTIS MONO, VERTIS MET, VERTIS SITA2, and VERTIS FACTORIAL studies), and one active-controlled, noninferiority trial was 52 weeks in duration (VERTIS SU study).

The available evidence on the efficacy of ERT was limited by the relatively short duration of the five 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 to glimepiride, a sulfonylurea. There was no direct evidence comparing ERT to 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. 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-Dimension (EQ-5D) instrument
- 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 monotherapy, as add-on therapy to metformin, or in combination with metformin and sitagliptin, was associated with statistically significant reductions in A1C percentage after 26 weeks compared with placebo (least squares [LS] mean difference –0.7% to –1.2%). ERT plus sitagliptin (as add-on therapy to metformin) also showed statistically significant differences in A1C as 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% 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 –2.2 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 between ERT and comparator groups in the VERTIS MET, VERTIS FACTORIAL, and VERTIS SITA2 studies ranged from –2.8 mm Hg to –4.5 mm Hg, which the clinical expert consulted for this review considered were clinically relevant. Systolic blood pressure data from the VERTIS MONO or VERTIS SU trials were either not statistically significant or inconclusive due to 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 were not statistically significant or inconclusive in four of the five studies (VERTIS MONO, VERTIS SU, VERTIS FACTORIAL, VERTIS 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. The extension data suggests that the reduction in body weight may extend beyond 26 weeks, but given the limitations of these studies (attrition and exclusion of non-responders) it is difficult to draw conclusions from these data.

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 frequency of adverse events was similar between groups within trials and ranged from 42% to 56% in the 26-week studies and from 59% to 62% across treatment groups in the 52-week trial.
- Serious adverse events were reported by 1% to 4% of patients who receive placebo, 1% to 6% of those who received ERT (alone or with sitagliptin), and 1% to 3% of those who received sitagliptin or glimepiride. Similarly, the proportion of patients who stopped treatment due to adverse events was generally low (placebo: 1% to 3%; ERT: 1% to 5%; active control: 0.4% to 4%).
- The frequency of documented or symptomatic hypoglycemia was highest in the glimepiride group (19% to 27%), compared with 1% to 9% among those who received ERT, and 1% to 4% among 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 was inconclusive due to failure of a prior outcome in the statistical testing hierarchy.
- Genital mycotic infections were reported more frequency in women (5% to 23%) and men (2% to 6%) who received ERT than in those who received placebo, glimepiride, or sitagliptin (women: 1% to 6%; men: 0% to 1%).
- 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.

Indirect Treatment Comparisons

The manufacturer submitted two indirect treatment comparisons which compared ERT as monotherapy, or 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 weeks to 26 weeks in duration in adults with type 2 diabetes with an A1C > 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 both NMAs 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 increase the chances of finding no difference between drugs. Based on the results of the submitted indirect treatment comparison, ERT as monotherapy, or in combination with metformin for the treatment of type 2 diabetes is likely more efficacious than placebo. Little can be elucidated on the comparative efficacy to other SGLT2 inhibitors or the relative safety of the product.

Cost and Cost-Effectiveness

The submitted price of ERT is $2.45 per tablet for both 5 mg and 15 mg doses. At the recommended dose of one tablet daily, the daily cost is $2.45 or $894 annually per patient.

The manufacturer submitted a cost comparison assessing the daily cost of ERT to SGLT2 inhibitors. The manufacturer submitted two NMAs in the absence of direct comparisons of treatment efficacy for ERT to other SGLT2s. The manufacturer concluded that ERT was comparable in efficacy and safety to other SGLT2s, supporting the choice of analysis. The manufacturer reported daily cost savings of $0.17 to $0.31 compared with the publicly available prices of empagliflozin (10 mg dose or 25 mg daily) or canagliflozin (100 mg or 300 mg daily), and similar costs or cost savings compared with dapagliflozin, depending on the dose used ($2.45 per 5 mg tablet or $2.62 per 10 mg tablet).

CDR identified the following key limitations and issues for consideration with the manufacturer's submission:

- Potentially relevant comparators from other classes of antihyperglycemic drugs were not included in the manufacturer's economic submission.
- There is uncertainty regarding the comparative clinical effectiveness of ERT compared with other SGLT2s. CADTH clinical reviewers concluded that ERT as monotherapy or as add-on therapy was more effective than placebo and that it may have similar efficacy to other SGLT2 inhibitors. While ERT 15 mg was noninferior to glimepiride (a sulfonylurea), noninferiority was not met for ERT 5 mg versus glimepiride.
- Due to uncertainty regarding the comparative clinical effectiveness and included comparators, a cost-utility analysis may have been more appropriate to assess comparative costs and effects of ERT to other comparators.
- The estimated cost savings noted by the manufacturer may differ due to publicly available prices of comparators and the use of sitagliptin with ERT which was not included in the manufacturer's results.

At the current daily cost of $2.45, ERT is less costly or equivalent in cost to the publicly available prices of other SGLT2 inhibitors.

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.