CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

DAPAGLIFLOZIN / METFORMIN HYDROCHLORIDE (Xigduo — AstraZeneca Canada Inc.) Indication: Type 2 Diabetes

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that dapagliflozin/metformin (Xigduo) 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 dapagliflozin, to replace the individual components of dapagliflozin and metformin for those patients who:

- have inadequate glycemic control on metformin, a contraindication or intolerance to a sulfonylurea, and for whom insulin is not an option, or
- have inadequate glycemic control on metformin and insulin.

Condition:
The drug plan cost for the dapagliflozin/metformin fixed-dose combination (FDC) should not exceed the combined cost of dapagliflozin and metformin administered separately.

Reasons for the Recommendation:

1. In study D1691C00007, dapagliflozin/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, Xigduo, reduces the overall pill burden and regimen complexity for patients who would have taken these medications individually.
2. In study D1691C00003, at 16 weeks, the dapagliflozin/metformin FDC was shown to achieve a statistically higher reduction of hemoglobin A1C compared with placebo and metformin. In addition, statistical significance was shown at 16 weeks for fasting plasma glucose, body weight, and the proportion of participants with a baseline hemoglobin A1C of ≥ 7% who achieved a hemoglobin A1C of < 7%.
3. Dapagliflozin/metformin FDC represents cost savings over the combination of the individual components. Annual cost savings range from [redacted] to [redacted] per patient.

Background:
Xigduo — an FDC of dapagliflozin and metformin hydrochloride — is indicated for use as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already being treated with dapagliflozin and metformin as separate tablets and achieving glycemic control.

Xigduo is also indicated as an adjunct to diet and exercise in adults with type 2 diabetes mellitus in the following scenarios:

- in combination with a sulfonylurea in patients who are already achieving glycemic control with dapagliflozin, metformin, and a sulfonylurea
- in combination with sitagliptin in patients who are already achieving glycemic control with dapagliflozin, metformin, and sitagliptin
- in combination with insulin in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin, and insulin.

Xigduo is available as 5 mg/850 mg and 5 mg/1,000 mg (dapagliflozin/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 review of manufacturer-provided information on the clinical evidence (bioequivalence, efficacy, and safety) for dapagliflozin/metformin hydrochloride, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

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 two surveys. The following is a summary of information provided by the patient group:

- Many patients using currently available therapies fail to achieve optimal glycemic control.
- Some patients find the administration of several medications problematic; any lack of adherence to dosing schedules contributes to suboptimal 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.
- Fluctuations in blood sugar can negatively affect a patient's ability to work and participate in social and family activities, and can interrupt a patient's 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, hypoglycemia, and other adverse effects.

Bioequivalence

- Study D1691C00007 was a pivotal Canadian, open-label, randomized, four-period, four-treatment, four-way crossover study conducted to determine the bioequivalence of the metformin immediate-release FDC tablet of dapagliflozin/metformin (5 mg/850 mg) (Xigduo) relative to single tablets of dapagliflozin (5 mg) and metformin (850 mg) administered together in healthy volunteers under fasted and fed conditions.
- The results from study D1691C00007 showed that the geometric mean ratios of the area under the curve (AUC) ($_{0\text{-}t}$) of both dapagliflozin and metformin are close to unity, and the corresponding 90% confidence interval for the treatment comparisons fall well within the limits of 0.8 and 1.25. The geometric mean ratios of C_{max} also fall within the limits of 0.8 and 1.25, and hence confirm the bioequivalence of each active ingredient in the FDC product to that of the individual components administered concomitantly under both fasted and fed conditions. The FDC tablet and individual tablets seems to have similar mean

concentration-time profiles under both fasted and fed conditions. This evidence supports the bioequivalence of Xigduo with metformin and dapagliflozin administered as separate tablets.

Clinical Trials

This CDR review included one double-blind (DB), placebo-controlled, multi-centre, randomized, parallel assignment phase 3 trial. Study D1691C00003 (N = 400) had a 16-week DB period that evaluated the efficacy and safety of dapagliflozin treatment regimens of 2.5 mg twice daily and 5 mg twice daily co-administered with metformin therapy, compared with placebo plus metformin in patients with type 2 diabetes treated with stable doses of metformin monotherapy ≥ 1,500 mg/day monotherapy for at least 10 weeks prior to enrolment who had A1C ≥ 6.7% and ≤ 10.5% at screening or A1C ≥ 6.5% and ≤ 10.0% one week prior to randomization.

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

- There was a statistically significant reduction from baseline in A1C at week 16 in the dapagliflozin 5 mg twice daily plus metformin group compared with the placebo plus metformin group (adjusted mean change versus placebo –0.35 [95% confidence interval (CI), –0.52 to –0.18]; *P* < 0.0001).
- The proportion of patients achieving a A1C < 7% at week 16 was a key secondary end point, and was statistically significantly greater in the dapagliflozin 5 mg twice daily plus metformin group compared with the placebo plus metformin group (38.2% versus 21.4%; adjusted mean difference versus placebo 16.8 [95% CI, 4.8 to 28.9]; *P* = 0.0062).
- There was a statistically significantly greater reduction from baseline in body weight at week 16 in the dapagliflozin 5 mg twice daily plus metformin group compared with the placebo plus metformin group (adjusted mean change versus placebo of –2.18 Kg [95% CI, –2.89 to –1.46]; *P* < 0.0001).
- There was a statistically significant reduction from baseline in FPG at week 16 in the dapagliflozin 5 mg twice daily plus metformin group compared with the placebo plus metformin group (adjusted mean change versus placebo –0.85 [95% CI, –1.19 to –0.51]; *P* < 0.001).

Harms (Safety and Tolerability)

- A total of 33% of patients in the dapagliflozin 5 mg twice daily plus metformin treatment group and 36.6% of patients in the placebo plus metformin treatment group reported an adverse event during the 16-week DB period.
- During the 16-week DB period, the proportion of patients reporting a serious adverse event was 1% in the dapagliflozin 5 mg twice daily plus metformin treatment group, and 0% of patients in the placebo plus metformin treatment group.
- During the 16-week DB period, there was no event of hypoglycemia in the dapagliflozin 5 mg twice daily plus metformin treatment group and placebo group.

Cost and Cost-Effectiveness
The manufacturer submitted a cost-minimization analysis comparing the drug costs of dapagliflozin/metformin FDC products including metformin and a dipeptidyl peptidase (DPP-4) inhibitor. At the submitted price of [redacted] per tablet ([redacted] per day), the average annual cost of dapagliflozin/metformin FDC ([redacted] per patient) was lower than the list prices of equivalent dose combinations of the individual components ($939 to $959 per patient, per year, excluding markups and dispensing fees). The daily cost of dapagliflozin/metformin FDC was also lower than the list prices of currently available DPP-4 inhibitor plus metformin FDC products ($2.54 to $3.23 daily).

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.

June 15, 2016 Meeting

Regrets:

One CDEC member did not attend.

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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