CDEC FINAL RECOMMENDATION

ALOGLIPTIN/METFORMIN
(Kazano – Takeda Canada Inc.)
Indication: Type 2 Diabetes Mellitus

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that alogliptin/metformin (ALO/MET) fixed-dose combination not be listed.

Reason for the Recommendation:
CDEC considered the single randomized controlled trial (RCT; study 305) comparing ALO with a sulfonylurea as add-on therapy to MET in patients with prior inadequate control with MET alone to have several significant limitations. Due to these limitations, and the lack of other relevant active-controlled clinical trials, the comparative clinical benefit of ALO relative to other less costly oral pharmacotherapies is uncertain for patients with type 2 diabetes with inadequate glycemic control on MET alone.

Background:
ALO/MET is indicated to improve glycemic control in adult patients with type 2 diabetes mellitus as follows: in patients inadequately controlled on MET; patients already being treated with the combination of ALO and MET; in combination with pioglitazone when pioglitazone and MET do not provide adequate glycemic control; and in combination with insulin, when insulin and MET do not provide adequate glycemic control. The current CADTH review is for use of ALO as an adjunct to diet and exercise in patients inadequately controlled on MET and in patients already being treated with the combination of ALO and MET.

ALO/MET is available as tablets containing 12.5 mg/500 mg, 12.5 mg/850 mg, and 12.5 mg/1,000 mg. For patients inadequately controlled on MET alone, the recommended dose of ALO/MET should provide ALO at 12.5 mg twice daily and MET at a similar dose (500 mg, 850 mg, or 1,000 mg twice daily) to that already being taken. For patients inadequately controlled on dual therapy with MET and pioglitazone, the dose of the thiazolidinedione should be maintained, and ALO/MET administered concomitantly; ALO should be dosed at 12.5 mg twice daily and MET at a similar dose (500 mg, 850 mg, or 1,000 mg twice daily) to that already being taken.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of ALO in combination with MET, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals living with type 2 diabetes.

Patient Input Information
The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- 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 impact patients' ability to work and participate in social and family activities, and they can interrupt normal activities of daily living.
- Diabetes, and the stigma associated with it, is associated with a psychological and emotional burden for patients.
- Many of the currently available therapies can cause significant weight gain and hypoglycemia.

Clinical Trials
The CDR systematic review included the following three RCTs:

- Study 008 (N = 500) was a 26-week, double-blind, placebo-controlled study comparing ALO 12.5 mg, ALO 25 mg, and placebo, all provided in combination with MET.
- Study 305 (N = 2,639) was a 104-week, double-blind, active-controlled, three-arm, non-inferiority trial comparing ALO 12.5 mg, ALO 25 mg, and glipizide (up to 20 mg per day), all provided in combination with MET.
- Study 302 (N = 784) was a 26-week, placebo-controlled, seven-arm, multi-centre RCT. Patients were randomized to one of seven treatment groups: ALO 12.5 mg twice daily plus MET 500 mg twice daily; ALO 12.5 mg twice daily/MET 1,000 mg twice daily; ALO 12.5 mg twice daily; ALO 25 mg once daily; MET 500 mg twice daily; MET 1,000 mg twice daily; or placebo.

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

- Glycemic control — change from baseline in glycated hemoglobin (A1C) and the proportion of patients with A1C less than 7% at end point.
- Body weight — change from baseline in body weight.
- Hypoglycemia — events of severe hypoglycemia and any hypoglycemia.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

In studies 008 and 302 the primary outcome was change from baseline in A1C at 26 weeks. The primary outcome of study 305 was change from baseline in A1C at 52 or 104 weeks, with a non-inferiority margin of 0.3%.

Efficacy

- ALO 12.5 mg and ALO 25 mg were superior to placebo for change from baseline in A1C at 26 weeks in study 008.
  - ALO 12.5 mg + MET versus placebo + MET: –0.4% (95% confidence interval [CI]: –0.6% to –0.2%)
  - ALO 25 mg + MET versus placebo + MET: –0.5% (95% CI, –0.7% to –0.3%).
- A greater proportion of patients in the ALO 12.5 mg group (51.6%) and ALO 25 mg group (44.4%) had A1C less than 7.0% at 26 weeks compared with the placebo group (18.3%) in study 008.
- Adjusted mean changes from baseline in body weight at 26 weeks were –0.4 kg, –0.7 kg, and –0.4 kg for ALO 12.5 mg, ALO 25 mg, and placebo groups respectively. There was no significant difference between the ALO and placebo groups:
  - ALO 12.5 mg + MET versus placebo + MET: 0.0 kg (95% CI, –0.7 to 0.7 kg)
  - ALO 25 mg + MET versus placebo + MET: –0.3 kg (95% CI, –0.9 to 0.4 kg).
- In study 305, ALO 12.5 mg and ALO 25 mg demonstrated non-inferiority compared with glipizide for change from baseline in A1C at 52 weeks and 104 weeks:
  - ALO 12.5 mg + MET versus glipizide + MET: –0.09% (1-sided 98.75% CI, 0.03%) at 52 weeks and –0.09% (1-sided 98.75% CI, 0.04%) at 104 weeks.
  - ALO 25 mg + MET versus glipizide + MET: –0.03% (1-sided 98.75% CI, 0.06%) at 52 weeks and –0.13% (1-sided 98.75% CI, –0.01%) at 104 weeks.
- Similar proportions of patients in the ALO 12.5 mg, ALO 25 mg and glipizide groups had A1C less than 7.0% (56.4%, 59.2% and 56.1% respectively) at 52 weeks and 104 weeks (45.6%, 48.5%, and 42.8% respectively) in study 305.
- Adjusted mean differences in body weight between ALO 12.5 mg and ALO 25 mg versus glipizide were statistically significant (–1.51 kg [95% CI, –1.79 to –1.23] and –1.58 kg [95% CI, –1.86 kg to –1.30 kg] respectively) in study 305.
- In study 302, both ALO 12.5 mg/MET 500 mg twice daily and ALO 12.5 mg/MET 1,000 mg twice daily were associated with statistically significantly greater reductions from baseline in A1C at 26 weeks versus the respective doses of MET monotherapy (–0.6% [97.5% CI, –0.9 to –0.3] and –0.4% [97.5% CI, –0.7 to –0.2%] respectively).

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one serious adverse event was:
  - Study 008: ALO 12.5 mg + MET (3.9%), ALO 25 mg + MET (2.8%), and placebo + MET (3.8%).
  - Study 305: ALO 12.5 mg + MET (9.9%), ALO 25 mg + MET (11%), and glipizide + MET (9.3%).
  - Study 302: ALO 12.5 mg/MET 500 mg twice daily (1.9%), ALO 12.5 mg/MET 1,000 mg twice daily (1.8%), MET 500 twice daily (1.8%), MET 1,000 mg twice daily (1.8%), and placebo (2.8%).
- The proportion of patients who experienced at least one adverse event was:
  - Study 008: ALO 12.5 mg (62.9%), ALO 25 mg (57.0%), and placebo (66.3%).
  - Study 305: ALO 12.5 mg (78.9%), ALO 25 mg (79.8%), and glipizide (77.8%).

  - Study 302: ALO 12.5 mg/MET 500 mg twice daily (63.2%), ALO 12.5 mg/MET 1,000 mg twice daily (64.0%), MET 1,000 mg twice daily (62.2%), MET 500 mg twice daily (68.8%), and placebo (71.7%).
- The proportion of patients who withdrew from the studies as a result of adverse events was:
  - Study 008: ALO 12.5 mg + MET (3.3%), ALO 25 mg + MET (1.9%), and placebo + MET (1.0%).
  - Study 305: ALO 12.5 mg + MET (6.8%), ALO 25 mg + MET (8.4%), and glipizide + MET (9.4%).
  - Study 302: ALO 12.5 mg /MET 500 mg twice daily (4.7%), ALO 12.5 mg/MET 1,000 mg twice daily (9.6%), MET 1,000 mg twice daily (1.8%), MET 500 mg twice daily (2.8%), and placebo (4.7%).
- The proportion of patients who experienced at least one hypoglycemic event was:
  - Study 008: ALO 12.5 mg + MET (0.9%), ALO 25 mg + MET (0%), and placebo + MET (2.9%)
  - Study 305: ALO 12.5 mg + MET (2.5%), ALO 25 mg + MET (1.4%), and glipizide + MET (23.2%)
  - Study 302: ALO 12.5 mg/MET 500 mg twice daily (1.9%), ALO 12.5 mg/MET 1,000 mg twice daily (5.3%), MET 1,000 mg twice daily (6.3%), MET 500 mg twice daily (1.8%), and placebo (1.8%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing ALO/MET (12.5 mg/500 mg, 12.5 mg/850 mg, or 12.5 mg/1,000 mg) with the individual components of ALO and MET, as well as the three other dipeptidyl-peptidase-4 (DPP-4 inhibitor and MET fixed-dose combinations available in Canada: linagliptin [LINA]/MET [2.5 mg/500 mg, 2.5 mg/850 mg, or 2.5 mg/1,000 mg], saxagliptin [SAXA]/MET [2.5 mg/500 mg, 2.5 mg/850 mg, or 2.5 mg/ 1,000 mg], and sitagliptin [SITA]/MET [50 mg /500 mg, 50 mg/850 mg, or 50 mg /1,000 mg]) for patients with type 2 diabetes. The manufacturer assumed the prescriber had determined that the most appropriate drug class to be used was a DPP-4 inhibitor, on a background of MET. Therefore, the comparators included in the base case were only the other marketed DPP-4 inhibitors plus MET combinations (and individual components). The cost-minimization analysis only considered drug acquisition costs that were obtained from the manufacturer (ALO/MET), IMS Brogan (LINA/MET and SAXA/MET), and the Ontario Drug Benefit Formulary (SITA/MET).

The assumption of similar efficacy and safety was based on two manufacturer-funded network meta-analyses (NMAs) comparing effects of each of the combination therapies in terms of A1C change from baseline; and the percentage of patients achieving target A1C less than 7%, weight, and hypoglycemic events. The NMAs suggested that there are no differences among DPP-4 inhibitors on A1C, body weight, and hypoglycemia.

CDR identified the following key limitations with the manufacturer's economic submission:

- The manufacturer did not consider the comparative efficacy and cost-effectiveness of ALO with that of other oral therapies that can be used as add-on to MET and are less expensive than DPP-4 inhibitors (sulfonylureas and pioglitazone).
- There was heterogeneity among trials included in the NMA in baseline characteristics and study durations.

- The primary outcome in most studies was change in A1C from baseline; thus it remains unclear whether the outcomes for body weight and hypoglycemic events were adequately powered in the respective studies to detect meaningful differences.

At the submitted price of $1.37 per tablet ($2.74 per day) ALO/MET costs less than SITA/MET ($3.20 daily), the same as SAXA/MET ($2.74 per day), and more than LINA/MET ($2.67 per day). ALO/MET costs the same as the individual components of ALO and MET when the daily dose of MET is 1,000 mg per day and less than the individual components when the daily dose of MET is greater than 1,000 mg per day (i.e., cost saving of $0.05 to $0.12 per day).

Other Discussion Points:
CDEC noted the following:

- The manufacturer's pharmacoeconomic analysis focused on comparing ALO against other DPP-4 inhibitors; however, CADTH's *Optimal Use Recommendations for Second- and Third-Line Therapy for Patients with Type 2 Diabetes* issued in 2013 indicate that a sulfonylurea is the preferred option for patients inadequately controlled on MET monotherapy.
- CADTH's *Optimal Use Recommendations for Second- and Third-Line Therapy for Patients with Type 2 Diabetes* indicate that a DPP-4 inhibitor may be added to MET and sulfonylurea combination therapy in circumstances where patients are unable to use insulin as a third-line option. ALO does not have a Health Canada–approved indication for use in combination with MET and a sulfonylurea.
- The included studies were not designed to examine the effects of ALO on microvascular or macrovascular outcomes, and the relationship between A1C and vascular outcomes is uncertain.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- Direct or indirect comparisons assessing the comparative efficacy of ALO versus other antihyperglycemic drugs for the prevention of macrovascular and microvascular diabetes-related complications; such comparisons are needed.

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

December 10, 2014 Meeting

Regrets:
None

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing 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.

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