CDEC FINAL RECOMMENDATION

ALOGLIPTIN (Nesina – Takeda Canada Inc.)
Indication: Type 2 Diabetes Mellitus

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that alogliptin (ALO) not be listed.

Reason for the Recommendation:
CDEC considered the single randomized controlled trial (RCT; study 305) comparing ALO with a sulfonylurea (SU) as add-on therapy to metformin (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 or an SU alone.

Background:
ALO is an oral antihyperglycemic drug belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class indicated for patients with type 2 diabetes to improve glycemic control as monotherapy (when MET is inappropriate due to contraindications or intolerance), in combination with MET, in combination with an SU, in combination with pioglitazone, in combination with pioglitazone and MET, and in combination with insulin (with or without MET). The current CADTH Common Drug Review (CDR) submission for ALO is for the following two indications: use in combination with MET when diet and exercise plus MET alone do not provide adequate glycemic control; and use in combination with an SU when diet and exercise plus an SU alone do not provide adequate glycemic control.

ALO is available as 6.25 mg, 12.5 mg, and 25 mg tablets. The recommended dose is 25 mg once daily for patients with no or mild renal impairment, 12.5 mg once daily for patients with moderate renal impairment, and 6.25 mg once daily for patients with severe renal impairment or end-stage renal disease requiring hemodialysis.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CDR: a systematic review of RCTs of ALO, 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 available therapies can cause significant weight gain and hypoglycemia.

Clinical Trials

The CDR systematic review included the following four RCTs:

- Study 007 (N = 500) was a 26-week, double-blind, placebo-controlled study comparing ALO 12.5 mg once daily, ALO 25 mg once daily, and placebo, all provided in combination with an SU.
- 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 007, 008 and 302-MET the primary outcome was change from baseline in A1C at 26 weeks. The primary outcome of study 305 was change from baseline A1C at 52 or 104 weeks, with a non-inferiority margin of 0.3%.

Efficacy

<u>Sulfonylurea Combination Therapy (Study 007)</u>

- ALO 12.5 mg and ALO 25 mg, both in combination with glyburide, demonstrated superiority for change from baseline in A1C at 26 weeks compared with placebo plus SU. The least squares mean differences (LSMD) were:

  - ALO 12.5 mg + SU versus placebo + SU: –0.4% (95% CI, –0.6 to –0.2%)
  - ALO 25 mg + SU versus placebo + SU: –0.5% (95% CI, –0.7 to –0.3%).
- A greater proportion of patients in the ALO 25 mg (34.8%) and ALO 12.5 mg groups (29.6%) had A1C less than 7.0% at 26 weeks compared with the placebo group (18.2%).
- Adjusted mean changes from baseline in body weight at 26 weeks were 0.6 kg, 0.7 kg, and –0.2 kg for the ALO 12.5 mg, ALO 25 mg, and placebo groups respectively. Mean differences between ALO 12.5 mg and ALO 25 mg, and placebo were statistically significant:
  - ALO 12.5 mg + SU versus placebo + SU: 0.8 kg (95% CI, 0.14 to 1.46)
  - ALO 25 mg + SU versus placebo + SU: 0.9 kg (95% CI, 0.21 to 1.54).

<u>Metformin Combination Therapy (Studies 008, 305, and 302-MET)</u>

- 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% 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 in baseline 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 (LSMD: –1.51 kg [95% CI, –1.79 to –1.23] and –1.58 kg [95% CI, –1.86 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 (LSMD: –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 007: ALO 12.5 mg + SU (5.4%), ALO 25 mg + SU (5.6%), and placebo + SU (2.0%).

  - 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 007: ALO 12.5 mg + SU (63.4%), ALO 25 mg + SU (63.1%), and placebo + SU (53.5%).
  - 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 007: ALO 12.5 mg + SU (2.5%), ALO 25 mg + SU (2.0%), and placebo + SU (2.0%).
  - 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 007: ALO 12.5 mg + SU (15.8%), ALO 25 mg + SU (9.6%), and placebo + SU (11.1%).
  - 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 (6.25 mg, 12.5 mg, and 25 mg) with other DPP-4 inhibitors (linagliptin 5 mg, saxagliptin 5 mg, and sitagliptin 100 mg) in patients with type 2 diabetes during a one-year time frame. The manufacturer only considered DPP-4 inhibitors as comparators in the base-case analysis based on the assumption that a prescriber would have already determined that a DPP-4 inhibitor is the most appropriate treatment option. Only drug acquisition costs were considered and these were obtained from the Ontario Drug Benefit Formulary.

The assumption of similar efficacy and safety was based on two manufacturer-funded network meta-analyses (NMAs) comparing the effects of each DPP-4 inhibitor used in combination with

MET or an SU 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 available as second-line treatment of type 2 diabetes such as MET, SUs, and thiazolidinediones.
- There was heterogeneity among trials included in the NMAs 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 recommended dose of 25 mg daily, when compared with other DPP-4 inhibitors, ALO ($2.62 daily) costs less than sitagliptin 100 mg ($2.95 daily) and saxagliptin 5 mg ($2.84 daily), but costs more than linagliptin 5 mg ($2.25 to $2.55 daily). ALO is more costly than the most frequently used oral treatments added-on to MET (SUs, $0.03 to $0.51 daily) or added-on to an SU (MET, $0.18 to $0.23 daily).

Other Discussion Points:

CDEC noted the following:

- CDEC noted the following key limitations with study 305: the use of a comparator that is not marketed in Canada (i.e., glipizide); upward titration of the glipizide dose was only permitted until week 20 of the 104 week trial; the titration algorithm resulted in less than 6.5% of the study population receiving an increased dose of glipizide; and the mean dosage of the comparator (5.2 mg) was well below the maximum recommended dose (i.e., 40 mg per day).
- 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 an SU 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 SU 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 an SU.
- 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.

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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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