Alogliptin: A new dipeptidyl peptidase-4 inhibitor for the management of type 2 diabetes mellitus

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According to the Centers for Disease Control and Prevention, diabetes affects about 25.6 million people age 20 years or older, or 11.3% of the U.S. population. Diabetes is the seventh leading cause of death in the United States. Overall, the risk of death among people with diabetes is about twice that of people of similar age but without diabetes. Diabetes is also a major cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults in the United States. Diabetes is also a major cause of heart disease and stroke. In 2007, the total estimated cost of diabetes was $174 billion, including $116 billion in medical expenditures and $58 billion in lost productivity. In 2007, people diagnosed with diabetes incurred average medical expenditures of $11,744 per year, two to three times higher than expenditures for persons without diabetes.

Management of diabetes varies depending on the type. Generally, insulin therapy is required for type 1 diabetes, while type 2 diabetes requires lifestyle modifications, oral or injectable hypoglycemic agents, and, in many cases, insulin. Several classes of oral hypoglycemic agents have been employed in the management of type 2 diabetes. The goal of treatment is to achieve the glycosylated hemoglobin (HbA1c) level of <7% recommended by the American Diabetes Association (ADA) for most patients to minimize the risk of microvascular complications.

ADA and the European Association for the Study of Diabetes (EASD), adjustment of therapy should be based on the HbA1c level and a change in therapy is recommended when HbA1c is above 7%. Due to the adverse effects of the available classes of drugs, there is a need for the development of drugs devoid of these negative effects.
unwanted adverse events, hence the development of new diabetes drugs.

Since 2006, different dipeptidyl peptidase (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin) have been approved for use in different countries for the management of diabetes mellitus. The algorithms developed by ADA/EASD in 2012 have recommended the use of DPP-4 inhibitors in two or three drug combinations for the management of type 2 diabetes on the basis of alogliptin's intermediate efficacy, weight neutrality, low risk of hypoglycemia, and rare adverse effects.

Alogliptin (Nesina, Takeda Pharmaceuticals) was recently approved by the Food and Drug Administration (FDA). Approved simultaneously with alogliptin were Takeda's alogliptin combinations with metformin (Kazano) and with pioglitazone (Oseni). This article reviews the pharmacology, pharmacodynamics, pharmacokinetics, safety, efficacy, and place in therapy of alogliptin in the management of type 2 diabetes mellitus.

Pharmacology

Alogliptin benzoate is a quinazoline-based, noncovalent DPP-4 inhibitor. It is a highly selective inhibitor (>10,000-fold selectivity for DPP-4 compared with DPP-2, -8, and -9) with sustained inhibition of DPP-4 activity, causing 2-fold to 3-fold increases of glucagonlike peptide 1 (GLP-1) levels. Plasma DPP-4 activity is inhibited by over 80% 24 hours after administration of alogliptin. The DPP-4 inhibitors enhance glucose-dependent insulin secretion from pancreatic β cells by preventing DPP-4-mediated degradation of endogenously released incretin hormones. The incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, mainly GLP-1, released in the presence of glucose or nutrients in the gut. Since these actions are glucose-concentration dependent, incretin-based drugs cause little or no hypoglycemic events. Compared with GLP-1 analogs, DPP-4 inhibitors are weight neutral and have no effects on gastric emptying.

The intestinal enteroendocrine L cell is the major source of the gut hormone GLP-1 in the human body. The secretion of GLP-1 by the ileal L cell is dependent on the presence of nutrients (carbohydrates, proteins, and lipids) in the lumen of the small intestine. GLP-1 stimulates glucose-dependent insulin release and may promote preservation of β-cell function in patients with type 2 diabetes. Active GLP-1 is rapidly cleaved by the widely expressed enzyme DPP-4 after secretion, such that the half-life of bioactive GLP-1 is less than three minutes. GLP-1 also affects kidney function by stimulating the renal excretion of fluid and sodium.

DPP-4 inhibitors were developed on the basis of the crystal structure of the DPP-4 molecule and precise knowledge about the amino acid residues that form the catalytic site. Alogliptin (designed based on radiographic information about the interactions of aminopiperidine and cyanobenzyl groups to the active site of DPP-4) forms noncovalent interactions with residues in the catalytic site of the DPP-4 molecule. Alogliptin is a potent inhibitor with low nanomolar 50% inhibitory concentration values that competitively and reversibly binds to the active site of DPP-4.

Pharmacokinetics

Alogliptin has a moderate degree of absorption, estimated to exceed 75%, and its absorption is not affected by food. It is rapidly absorbed after oral administration, with a peak plasma concentration (Cmax) of 110 ± 26 ng/mL, a time to reach Cmax (tmax) of 2 hours, and an area under the concentration–time curve (AUC) of 12,231 ± 21 ng·hr/mL after the administration of a 25-mg dose in healthy multiparous or racially uncharacterized volunteers. In multiparous or racially uncharacterized North American or European patients with type 2 diabetes, alogliptin had a Cmax of 146 ± 59 ng/mL, a tmax of 1.3 hours, and an AUC of 1,058 ± 165 ng·hr/mL after receiving a 25-mg dose. In healthy Japanese volunteers given a dose of 12.5 mg, the Cmax was 97 ng/mL, the tmax was 1.0 hour, and the AUC was 851 ng·hr/mL. Alogliptin is 20% protein bound and has an apparent volume of distribution of 561 ± 106 L.

Alogliptin undergoes about 10% hepatic metabolism, since approximately 87% of the plasma radioactivity and 95% of urine radioactivity are accounted for by the parent compound; metabolites (nine demethylated and acetylated) are detected in small amounts (<5% of the dose) with little or no pharmacologic activity. In healthy multiparous volunteers, the elimination half-life (t1/2) was 21.1 ± 4.4 hours, and the apparent oral clearance (CL/F) was 0.24 ± 0.02 L/hr/kg compared to a t1/2 of 21.1 ± 8.8 hours and a CL/F of 0.24 ± 0.03 L/hr/kg for multiparous or racially uncharacterized North American or European patients with type 2 diabetes mellitus, which supports once-daily oral dosing. The most common excretion pathway for DPP-4 inhibitors is through the kidneys, with 63.3% ± 4.0% of alogliptin excreted unchanged (renal clearance of 201 ± 29 mL/min) and about 11% excreted fecally.

A single oral dose of alogliptin 25–800 mg dependently inhibited plasma DPP-4 activity in healthy male volunteers, with peak inhibition exceeding 93% and ranging from 74.3% to 97.0% 24 hours after administration and from 47.5% to 83.0% 72 hours after administration. All doses of alogliptin increased intact GLP-1 levels by twofold to threefold compared with placebo.
Age, sex, and race do not appear to affect the clinical pharmacokinetics of alogliptin.\textsuperscript{47,48,52,65,99,24}

No drug interactions are known to be associated with alogliptin monotherapy.\textsuperscript{8} Alogliptin does not require any dosage adjustment when coadministered with ketoconazole, fluconazole, gemfibrozil, warfarin, metformin, glyburide, and pioglitazone.\textsuperscript{47,48,22}

**Clinical efficacy**

In patients with type 2 diabetes, alogliptin monotherapy for 14 days (25, 100, or 400 mg/day) decreased DPP-4 activity by 81.8–96.7% and 66.3–81.6% at 24 and 72 hours after administration on day 14, respectively, across all doses.\textsuperscript{67,98} In a randomized controlled trial, Kutoh and Ukai\textsuperscript{8} showed glycemic efficacy with the reduction of HbA\textsubscript{1c} from 10.51% to 8.74%, increased levels of homeostasis model assessment-B, decreased levels of atherogenic lipid, and no change in body mass index (BMI) after three months of alogliptin monotherapy 12.5–25 mg/day without any clinically adverse events. Mild hypoglycemic events that could be managed by consuming glucose drinks alone were reported in 16% of subjects.

**Monotherapy.** A randomized, double-blind, placebo-controlled study was conducted to evaluate the use of alogliptin in patients with treatment-naïve type 2 diabetes.\textsuperscript{42} Patients were randomized to receive alogliptin 12.5 mg (n = 133), alogliptin 25 mg (n = 131), or placebo (n = 65). No other antidiabetics were permitted. Eligible patients had to be 18–80 years old with an HbA\textsubscript{1c} between 7–10%, a BMI of 23–45 kg/m\textsuperscript{2}, and a blood pressure measurement of <180/110 mm Hg. No exclusion criteria were mentioned. The primary endpoint was the reduction in HbA\textsubscript{1c} from baseline to week 26. Mean HbA\textsubscript{1c} levels decreased by −0.56%, −0.59%, and −0.02% in the alogliptin 12.5-mg, alogliptin 25-mg, and placebo groups, respectively (p < 0.001 compared with placebo). The rate of hypoglycemia was 1.5–3.9%, with no severe episodes reported. Headache was the only adverse effect that occurred at a higher rate compared with placebo (6.8–7.5% versus 4.7%). The authors concluded that alogliptin produced clinically important reductions in HbA\textsubscript{1c} levels.

**Monotherapy or combination therapy with pioglitazone.** A double-blind, parallel-group Phase III trial was conducted to compare the efficacy and tolerability of initial therapy with alogliptin monotherapy, pioglitazone monotherapy, and alogliptin and pioglitazone combination therapy.\textsuperscript{49,50} Patients with treatment-naïve type 2 diabetes mellitus (n = 654) were randomized into four treatment groups: alogliptin 25 mg daily, pioglitazone 30 mg daily, alogliptin 12.5 mg and pioglitazone 30 mg daily, and alogliptin 25 mg and pioglitazone 30 mg daily. Eligible patients could not have taken any antihyperglycemic agent within three months of screening and had to have been unsuccessful with lifestyle modifications (diet and exercise) for at least two months. The participants had to be 18–80 years old, have type 2 diabetes, and have an HbA\textsubscript{1c} value of 7.5–11%. No exclusion criteria were mentioned.

Patients had a mean age of 53 years, and 51.1% were women. The mean baseline HbA\textsubscript{1c} level was 8.8%, the mean BMI was 31 kg/m\textsuperscript{2}, and the mean duration of diabetes diagnosis was 3 years. The primary endpoint was the change in HbA\textsubscript{1c} from baseline to week 26. All four groups had reductions in HbA\textsubscript{1c} values at 26 weeks: −0.96% ± 0.081% reduction in the alogliptin 25-mg group, −1.15% ± 0.083% in the pioglitazone 30-mg group, −1.56% ± 0.081% in the alogliptin 12.5-mg plus pioglitazone 30-mg group, and −1.71% ± 0.081% in the alogliptin 25-mg plus pioglitazone 30-mg group. The reduction in the alogliptin 25-mg plus pioglitazone 30-mg group was statistically significant compared with groups receiving alogliptin or pioglitazone monotherapy (p < 0.05). The mean reduction in HbA\textsubscript{1c} in the alogliptin 12.5-mg plus pioglitazone 30-mg group was significantly higher than in the pioglitazone monotherapy group (p < 0.05) but not the alogliptin monotherapy group. The rate of adverse effects was the highest in the alogliptin 25-mg plus pioglitazone 30-mg group and lowest in the alogliptin monotherapy group. The alogliptin 25-mg plus pioglitazone 30-mg group had the highest rate of hypoglycemia (3%).

**Combination therapy with metformin.** A double-blind, randomized, placebo-controlled trial was conducted to evaluate the efficacy of alogliptin in patients whose diabetes was inadequately controlled with metformin alone.\textsuperscript{51} Patients were randomized 2:2:1 to receive alogliptin 12.5 mg (n = 213), alogliptin 25 mg (n = 210), or placebo (n = 104) in addition to their metformin therapy after a four-week run-in period. To qualify for the study, patients had to have type 2 diabetes and an HbA\textsubscript{1c} value of 7–10% despite metformin therapy at a dose of 1500 mg or greater for at least eight weeks. Patients who used glucocorticoids or any weight-loss agents within the three months before randomization were excluded, as were patients with recent coronary events or a history of cancer. The mean HbA\textsubscript{1c} of the study population was 7.9–8%, and their mean fasting plasma glucose (FPG) concentration ranged from 168 to 180 mg/dL. The mean age of patients was 55 years, and there was equal representation of men and women who had a diagnosis of diabetes for a mean of 6 years. Patients requiring hyperglycemic rescue based on predetermined criteria were considered to have completed the study. The primary endpoint was the change in HbA\textsubscript{1c} from baseline to week 26. At week 26, HbA\textsubscript{1c} decreased from baseline by 0.6%, 0.6%, and 0.1% in

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the alogliptin 12.5-mg, alogliptin 25-mg, and placebo groups, respectively. FPG reductions were significantly greater in both alogliptin groups compared with placebo (p < 0.001). Alogliptin was associated with a low rate of hypoglycemia and proved to be weight neutral, as there was no notable difference in weight in the alogliptin groups compared with placebo. The authors concluded that alogliptin was a safe and effective option in patients whose diabetes was not adequately controlled with metformin alone.

Combination therapy with metformin and pioglitazone. A randomized, double-blind, active-controlled, parallel study assessed the efficacy of adding alogliptin 25 mg (n = 404) versus adding an additional 15 mg of pioglitazone (n = 399) to the regimen of patients treated with both metformin and pioglitazone 30 mg.25 The study population included patients with type 2 diabetes and an HbA1c of 7.0–10% on a maximum tolerated dose of metformin (≥1500 mg or maximum tolerated dose) and pioglitazone 30 mg. Patients with recent coronary events or a history of cancer were excluded. The majority of patients were white, had a mean age of 55.1 years, and had a diabetes diagnosis for a mean of 7.2 years. The mean HbA1c values at baseline were 8.3% in the metformin, pioglitazone, and alogliptin 25-mg group and 8.1% in the metformin and pioglitazone 45-mg group. The primary endpoint was the change from baseline in HbA1c value at weeks 26 and 52. A per-protocol analysis showed a −0.89% and a −0.70% change in HbA1c in the metformin, pioglitazone, and alogliptin 25-mg group after 26 and 52 weeks, respectively, and a −0.42% and a −0.29% change in the metformin and pioglitazone 45-mg group after 26 and 52 weeks, respectively (p < 0.001). The proportion of patients achieving an HbA1c goal of ≤7% or ≤6.5% was higher in the metformin, pioglitazone, and alogliptin 25-mg group compared with the metformin and pioglitazone 45-mg group. FPG concentrations were also higher in the metformin, pioglitazone, and alogliptin 25-mg group compared with the metformin and pioglitazone 45-mg group. Although the rate of discontinuation was similar between groups, more patients experienced hypoglycemia in the metformin, pioglitazone, and alogliptin group (n = 18) compared with the dual-therapy group (n = 6). The authors concluded that the addition of alogliptin was preferred over increasing the dose of pioglitazone. An intent-to-treat analysis would have been more appropriate, as the sample size of 760 needed to declare noninferiority was not met; only 526 patients completed the trial.

Combination therapy with insulin. A double-blind, randomized, placebo-controlled trial was conducted over a 26-week period to assess the efficacy and safety of alogliptin when added to insulin.26 Participants were randomized to receive alogliptin 12.5 mg, alogliptin 25 mg, or placebo after a four-week run-in period. Patients were included if they had type 2 diabetes that was inadequately controlled on a stable dose of insulin alone or in combination with metformin. A stable dose of insulin was defined as 15–100 units daily for at least 8 weeks before randomization. Patients had to have an HbA1c value of ≥8% and a BMI of 23–45 kg/m² to be included in the trial. Patients who used glucocorticoids or any weight loss agents within the three months before randomization were excluded, as were patients with recent coronary events or a history of cancer. A total of 390 patients were enrolled in the study (mean age, 55 years; mean HbA1c value, 9.3%) and randomized to one of three different groups. While all patients included in the study were on insulin, approximately 60% of patients were also on metformin. Of note, patients requiring hyperglycemic rescue based on predetermined criteria were considered to have completed the study. The primary endpoint was the change from baseline HbA1c at week 26. At 26 weeks, HbA1c changes from baseline were −0.63%, −0.71%, and 0.13% for the alogliptin 12.5-mg, alogliptin 25-mg, and placebo groups, respectively (p < 0.001 compared with placebo). The changes in body weight and number of hypoglycemia episodes were similar across all three groups at 26 weeks. The authors concluded that alogliptin was a viable option to be added to insulin therapy because it improved glycemic control in the study. Limited information was provided about insulin use and dosing during the 26-week trial.

Safety

Although the specific risk with alogliptin has not been determined, all DPP-4 inhibitors can cause pancreatitis and are not recommended for patients with a history of pancreatitis, gallstones, and hepatic or renal problems.27-29 Pancreatitis, pancreatic cancer, and thyroid cancer are the biggest concerns with the DPP-4 inhibitors. One study that examined the FDA’s database of reported adverse effects for DPP-4 inhibitors found an almost six times greater risk in patients who took sitagliptin or exenatide compared with other therapies.30 Studies assessing the efficacy and safety of alogliptin concluded that hypoglycemia was not noteworthy with alogliptin alone.31,23,24 Studies in which weight gain was evaluated found alogliptin to be weight neutral.

More data were required by FDA on cardiovascular safety for all new diabetes medications in 2009, thereby delaying the release of alogliptin on the U.S. market. With the drug’s approval in January 2013, FDA is requiring five postmarketing studies for alogliptin: (1) a cardiovascular outcomes trial, (2) an enhanced pharmacovigilance program to monitor for liver abnormalities,
serious cases of pancreatitis, and severe hypersensitivity reactions, (3) a pediatric dose-finding study, (4) a pediatric safety and efficacy study of alogliptin monotherapy, and (5) a pediatric safety and efficacy study of the combination of alogliptin and metformin. Although alogliptin has only been on the U.S. market since 2013, it has been on the Japanese market since 2010 and in Europe since 2012, so long-term data may be more readily available from these sources. Given that the results of these trials are not yet available, other medications that have undergone more testing should be chosen over alogliptin.

Dosage and administration
Alogliptin. The usual starting dose of alogliptin is 25 mg per day. It is intended for oral use and can be taken with or without food.27 No dose adjustment of alogliptin is necessary for patients with mild renal impairment (creatinine clearance \( \text{CL}_{\text{cr}} \) of \( \geq 60 \) mL/min). The

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*Data obtained from Micromedex Health care Series. DrugDEX system. Greenwood Village, CO:Truven Health Analytics. Updated periodically.
The recommended dosage of alogliptin is 12.5 mg once daily for patients with moderate renal impairment (CLCR of ≥30 to <60 mL/min). The recommended dosage of alogliptin is 6.25 mg once daily for patients with severe renal impairment (CLCR of ≥15 to <30 mL/min) or with end-stage renal disease (CLCR of <15 mL/min or requiring hemodialysis). Alogliptin may be administered without regard to the timing of dialysis, as only 7% of the drug is removed by dialysis. Alogliptin has not been studied in patients undergoing peritoneal dialysis. Because there is a need for dosage adjustment based on renal function, assessment of renal function is recommended before initiating alogliptin therapy and periodically thereafter. No dosage adjustment is recommended for alogliptin when initiating treatment in diabetic patients with hepatic impairment.21

Alogliptin and pioglitazone. The alogliptin and pioglitazone combination drug should be taken once daily and can be taken without regard to food. The tablets must not be split before swallowing. The combination of alogliptin and pioglitazone comes in six different strengths: 25 mg of alogliptin plus 15, 30, or 45 mg of pioglitazone, and 12.5 mg of alogliptin plus 15, 30, or 45 mg of pioglitazone. The dose can be increased to a maximum of alogliptin 25 mg/pioglitazone 45 mg once daily based on glycemic response as determined by HbA1c value. After initiation or after increasing the dose, patients should be monitored carefully for adverse reactions related to fluid retention as has been seen with pioglitazone (e.g., weight gain, edema, signs and symptoms of congestive heart failure).28

Alogliptin–metformin combination. Alogliptin and metformin should be taken twice daily with food with gradual dose escalation to reduce the adverse gastrointestinal effects of metformin. The tablets must not be split before swallowing, and dosing may be adjusted based on effectiveness and tolerability but should not exceed the maximum recommended daily doses of alogliptin (25 mg) and metformin (2000 mg). Two formulations of this combination therapy are available (alogliptin 12.5 mg plus metformin 500 mg and alogliptin 12.5 mg plus metformin 1000 mg). Health care providers should individualize the starting doses of alogliptin and metformin based on the patient’s current regimen.29

Place in therapy
ADA recommends the use of metformin as first-line therapy for the treatment of hyperglycemia in patients with type 2 diabetes. When metformin alone is inadequate, four treatment options are available: thiazolidinediones, injectable GLP-1 receptor agonists, DPP-4 inhibitors, and insulin replacement therapy.30 Compared with these other classes of medications, DPP-4 inhibitors have moderate efficacy, have a high cost, are weight neutral, and are associated with a low rate of hypoglycemia. There is no real distinction between the drugs in this class (Table 1). When the goal is to avoid weight gain or when hypoglycemia is a concern, DPP-4 inhibitors are recommended.31 None are available in generic form.32

Conclusion
Alogliptin, a selective DPP-4 inhibitor, does not differ greatly from the other DPP-4 inhibitors currently available. It can be used as monotherapy or in combination with metformin for the management of type 2 diabetes.

References


