Lixisenatide (Adlyxin)

A Once-Daily Incretin Mimetic Injection for Type-2 Diabetes

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INTRODUCTION

According to the Centers for Disease Control and Prevention, 29.1 million people in the United States have diabetes (approximately 9.3% of the nation's population), accounting for $245 billion in health care costs.[1] The increased prevalence of the disease over the last several decades, along with the economic burden, warrants great attention to clinical management.

Type-2 diabetes mellitus (T2DM) is a chronic condition with a complex pathophysiology characterized by pancreatic beta cell dysfunction and insulin resistance. This results in a decrease in insulin activity and consequentially elevated blood glucose levels in both the fasting and postprandial state. Patients with T2DM are also at an increased risk for both microvascular and macrovascular complications. Therefore, pharmacological therapy should seek to reduce blood glucose levels and lower the risk for such complications. The American Diabetes Association (ADA) recommends lowering blood glucose to a glycated hemoglobin (HbA_{1c}) target of less than 7% for most nonpregnant adult patients.[2] A more stringent target of less than 6.5% can be considered for the following patients: those who have had a short duration of diabetes, are treated with lifestyle modifications or metformin only, have a long life expectancy, or do not have significant cardiovascular disease. Conversely, a less stringent goal of less than 8% can be considered for those with a history of hypoglycemia, limited life expectancy, advanced DM-related complications, and severe comorbidities.

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Metformin continues to be the pharmacological agent recommended for initial T2DM therapy, in addition to lifestyle modifications and cardiovascular risk reduction. ADA guidance then promotes the use of a patient-centered approach to guide additional therapy considering efficacy, risk of hypoglycemia, weight changes, side effects, and cost with additional medication.[2] Six treatment options are available as add-on therapy to metformin: sulfonylureas (SUs), thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), or insulin.

Recently, incretin-based therapies, which include the DPP-4 inhibitors and the GLP-1 RAs, have come into favor over the traditional oral options of SUs and TZDs due to comparable efficacy, favorable effects on weight, and infrequent hypoglycemia.[3–6] This is primarily because they uniquely target gut hormones that play an important role in glucose homeostasis. Under normal conditions, the hormone GLP-1 stimulates insulin secretion from beta cells in the pancreas and decreases glucagon secretion from alpha cells, both in a glucose-dependent manner. In addition, GLP-1 inhibits gastric emptying in the stomach and exerts an effect on the central nervous system that increases satiety. Like GLP-1, another hormone known as glucose-dependent insulinotropic polypeptide (GIP) also stimulates insulin secretion from the pancreas. In patients with T2DM, both GLP-1 and GIP are significantly reduced, contributing to a blunted insulin secretory response.[7] In addition, native GLP-1 has a very short half-life due to rapid degradation and inactivation by the enzyme DPP-4, limiting the effect of native GLP-1 in patients with T2DM. Drug targets, therefore, have been developed to inhibit the DPP-4 enzyme and prolong the half-life of endogenous GLP-1, promoting a physiological response with the use of DPP-4 inhibitors. Drugs have also been developed to supply exogenous GLP-1 at supraphysiological doses using GLP-1 RAs, producing an amplified response.

A growing number of GLP-1 RAs have been introduced to the market since 2005. Structurally, they can be classified as exendin-based or human GLP-1-based.[7] Exendin-4 is a naturally occurring peptide derived from the venom of the Heloderma lizard. It has a 53% homology to human GLP-1 and is resistant to degradation by the DPP-4 enzyme. Beside homology to native GLP-1, there are also differences in the effect these drugs exert on pre- and postprandial glucose. Duration of action and the degree to which gastric emptying is slowed also account for differences. Finally, dosing, administration, storage, and tolerability can vary from one agent to the next.[8]

Six GLP-1 RAs have been approved for use in the United States: exenatide (Byetta, Amylin Pharmaceuticals), liraglutide (Victoza, Novo Nordisk), exenatide extended-release (Bydureon, Amylin Pharmaceuticals), albiglutide (Tanzeum, GlaxoSmithKline), dulaglutide (Trulicity, Eli Lilly), and most recently, in 2016, lixisenatide (Adlyxin, Sanofi-Aventis).[9–14] This article will focus on lixisenatide.

DESCRIPTION

Lixisenatide is a 44-amino acid peptide. Like exenatide, it is based on exendin-4 with a modification at the C-terminus—a deletion of a proline residue and the addition of six lysine residues.[15] It is amidated at the C-terminal amino acid (position 44).[14]

PHARMACODYNAMICS AND PHARMACOKINETICS

Lixisenatide has a high affinity for the GLP-1 receptor, up to four times greater

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than human GLP-1, and is approximately 55% bound to plasma proteins.[15,16] Following subcutaneous administration, the drug is absorbed rapidly, and time to maximal concentration has been reported at two hours. Elimination occurs primarily through glomerular filtration with a mean terminal half-life of approximately three hours.[14] The area under the plasma concentration curve has been shown to increase in patients with moderate-to-severe renal impairment. Lixisenatide does not affect the activity of cytochrome P450 isoenzymes.[14] However, the rate of absorption of orally administered drugs, such as acetaminophen, ethinyl estradiol, and warfarin, may be reduced because lixisenatide slows gastric emptying.[14–16] Despite this, no clinically significant adverse effects have been reported from concomitant use.[14]

CLINICAL TRIALS

GetGoal Overview

A series of randomized, controlled, phase 3 trials known as the GLP-1 Agonist AVE0010 in Patients with Type 2 Diabetes Mellitus for Glycemic Control and Safety Evaluation (GetGoal) program studied lixisenatide as monotherapy and in combination with other medications used to treat T2DM. The GetGoal trials were designed to establish the safety and efficacy of lixisenatide 20 mcg, administered as a once-daily injection, in patients with T2DM who were either treatment naïve or who had uncontrolled disease on oral antidiabetic agents with or without basal insulin.[17–27]

Collectively, these randomized, placebo- or active-controlled trials included patients with baseline HbA_{1c} of 7% to 10% and a fasting plasma glucose (FPG) of 250 mg/dL or less. Key exclusion criteria, consistent across all trials, included a history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, or inflammatory bowel disease; history of gastrointestinal disease with prolonged nausea and vomiting in the six months prior to study initiation; and end-stage renal disease (defined as creatinine clearance of less than 15 mL/min) and/or dialysis.[17–27] Depending on the trial, various exclusions were applied to the participants based on antihyperglycemic agents.

The primary endpoint for each GetGoal trial was the reduction in HbA_{1c} from baseline. Secondary endpoints, which were also consistent among all trials in the series, included percentage of patients achieving an HbA_{1c} of less than 7% and changes in body weight. Some trials also reported changes from baseline in FPG and two-hour postprandial plasma glucose (2-h PPG). These endpoints were measured over at least 24 weeks in all trials except the 12-week GetGoal-Mono trial. Table 1 contains a brief overview of key baseline demographics in the GetGoal studies.[17–27]

Table 1 GetGoal Clinical Program: Demographic Overview

Trial	Patients (N)	Mean Diabetes Duration (years)	Mean Baseline HbA_{1c} (%)	Mean FPG (mg/dL)	Mean BMI (kg/m^2)
GetGoal-Mono	361	1.3	8	162.7	31.9
GetGoal-Mono-Japan	69	7.3	8.3	171.2	25
GetGoal-M	680	6.1	8.1	169.1	32.9
GetGoal-F1	482	6	8	171.2	32.5
GetGoal-M-Asia	390	6.6	7.9	158.4	26.9
GetGoal-S	859	9.3	8.3	172	30.2
GetGoal-P	484	8.1	8.1	164	33.9
GetGoal-L	495	12.5	8.4	145.3	32.1
GetGoal-L-Asia	311	13.9	8.5	139	29
GetGoal-Duo 1	446	9.2	7.6	121	31.9
GetGoal-X	634	6.8	8	175	33.6

BMI = body mass index; FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin.

The eight GetGoal trials discussed in detail throughout this article were conducted mostly in North America and Europe with a predominantly Caucasian patient population. Of the more than 4,400 patients, roughly 49% were men. Collectively, the typical patient was about 56 years of age, obese with a body mass index (BMI) of 32.35 kg/m^2 (six of eight studies reported this metric), and had been diagnosed with T2DM for 7.6 years. These patients had a baseline HbA_{1c} of 8.2%, FPG of 162 mg/dL, and 2-h PPG of 278 mg/dL.[17,19,20,22–24,26,27] Three published GetGoal trials were conducted solely in East Asian and Pacific countries. Of these 770 patients, 52% were men. The typical patient was 56 years of age, overweight (BMI, 26.1 kg/m^2), and had been diagnosed with T2DM for 9.6 years. These patients had a baseline HbA_{1c} of 8.2%, FPG of 151 mg/dL, and 2-h PPG of 308 mg/dL.[18,21,25]

Lixisenatide as Monotherapy

The GetGoal-Mono trial assessed two methods of uptitrating lixisenatide to a target dose of 20 mcg daily. Both dosing schedules had patients start by subcutaneously injecting 10 mcg once daily. The lixisenatide one-step group increased the dose to 20 mcg daily after two weeks, while the two-step group increased to 15 mcg after one week before increasing to 20 mcg daily after week 2. Both titration schedules were compared with placebo and were used as monotherapy for treatment-naïve patients diagnosed with T2DM about 15 months prior. The primary endpoint of mean change in HbA_{1c} from baseline resulted in a reduction of 0.66% and 0.54% for the one-step and two-step titration schedules, respectively, compared with placebo ($P < 0.0001$). Significantly more patients taking lixisenatide 20 mcg (52% for the one-step dose increase and 47% for the two-step increase) achieved an HbA_{1c} goal of less than 7% compared with those taking placebo (27%). Both lixisenatide arms demonstrated some reduction in FBG compared with placebo, but more clinically meaningful differences in 2-h PPG were observed (Table 2).[17]

The GetGoal-Mono-Japan trial was conducted in Japan and utilized descriptive statistics while primarily assessing the safety of two-step versus one-step dose titration of lixisenatide. The open-label study utilized no placebo control; about

Table 2 GetGoal Clinical Program: Efficacy Results

Study Arms	Change in HbA_{1c} From Baseline	Change in FPG From Baseline	Change in 2-h PPG From Baseline*	Weight Loss
GetGoal-Mono (12 weeks)				
Placebo	–0.19%	4.5 mg/dL	–11.7 mg/dL	Body weight decreased by approximately 2.0 kg in all groups.
Lixisenatide 2-step dose titration	–0.73% ($P < 0.0001$)	–11.9 mg/dL ($P < 0.001$)	–81.2 mg/dL ($P < 0.0001$)	
Lixisenatide 1-step dose titration	–0.85% ($P < 0.0001$)	–15.7 mg/dL ($P < 0.001$)	–98.6 mg/dL ($P < 0.0001$)	
GetGoal-Mono-Japan (24 weeks)†				
Lixisenatide 2-step dose titration	–0.99%	–20.9 mg/dL	Not reported	–0.43 kg
Lixisenatide 1-step dose titration	–0.74%	–10.1 mg/dL		–1.08 kg
GetGoal-M (24 weeks)				
Metformin	–0.40%	–5.4 mg/dL	–25.2 mg/dL	–1.6 kg
Lixisenatide A.M. administration	–0.9% ($P < 0.0001$)	–21.6 mg/dL ($P < 0.0001$)	–106.3 mg/dL ($P < 0.0001$)	–2.0 kg
Lixisenatide P.M. administration	–0.8% ($P < 0.0001$)	–14.4 mg/dL ($P < 0.0046$)	Not reported	–2.0 kg
GetGoal-F1 (24 weeks)				
Metformin	–0.40%	–7.2 mg/dL	Not reported	–1.6 kg
Lixisenatide 2-step dose titration	–0.8% ($P < 0.0001$)	–19.8 mg/dL ($P < 0.001$)		–2.7 kg ($P < 0.01$)
Lixisenatide 1-step dose titration	–0.9% ($P < 0.0001$)	–21.6 mg/dL ($P < 0.001$)		–2.6 kg ($P < 0.01$)
GetGoal-M-Asia (24 weeks)				
Metformin ± sulfonylurea	–0.47%	–3.8 mg/dL	–24 mg/dL	–1.24 kg
Lixisenatide	–0.83% ($P = 0.0004$)	–12.4 mg/dL ($P = 0.0109$)	–101.1 mg/dL ($P < 0.0001$)	–1.5 kg
GetGoal-S (24 weeks)				
Sulfonylurea ± metformin	–0.10%	–1.8 mg/dL	2.1 mg/dL	–0.9 kg
Lixisenatide	–0.85% ($P < 0.0001$)	–16.7 mg/dL ($P < 0.0001$)	–108.1 mg/dL ($P < 0.0001$)	–1.7 kg ($P < 0.0001$)
GetGoal-P (24 weeks)				
Pioglitazone ± metformin	–0.50%	–5.4 mg/dL	Not reported	0.2 kg
Lixisenatide	–1% ($P < 0.0001$)	–19.9 mg/dL ($P < 0.0001$)		–0.2 kg
GetGoal-L (24 weeks)				
Established dose of basal insulin ± metformin	–0.30%	No change	–21.6 mg/dL	–0.5 kg
Lixisenatide	–0.6% ($P = 0.0002$)	–1.8 mg/dL	–97.3 mg/dL ($P < 0.0001$)	–1.8 kg ($P < 0.0001$)
GetGoal-L-Asia (24 weeks)				
Established dose of basal insulin ± sulfonylurea	0.11%	4.5 mg/dL	–2.5 mg/dL	–0.06 kg
Lixisenatide	–0.77% ($P < 0.0001$)	–7.6 mg/dL ($P = 0.0187$)	–143.4 mg/dL ($P < 0.0001$)	–0.38 kg

table continues

Table 2 GetGoal Clinical Program: Efficacy Results (continued)

Study Arms	Change in HbA_{1c} From Baseline	Change in FPG From Baseline	Change in 2-h PPG From Baseline*	Weight Loss
GetGoal-Duo 1 (24 weeks)				
Active titrated insulin glargine + metformin ± thiazolidinedione	–0.30%	4.3 mg/dL	1.8 mg/dL	1.2 kg
Lixisenatide	–0.6% ($P < 0.0001$)	1.7 mg/dL	–55.8 mg/dL ($P < 0.0001$)	0.3 kg ($P < 0.0012$)
GetGoal-X (24 weeks)				
Metformin + exenatide twice daily	–0.96%	–26.1 mg/dL	Not reported	–3.98 kg
Metformin + lixisenatide	–0.79%	–21.9 mg/dL		–2.96 kg

All *P* values relate to comparison of mean difference versus control group.

* All tests were conducted using a standardized meal.

† Only descriptive statistics were used in analyzing variables; results reported are from week 24.

half the patients were treatment naïve while the other half were taking an oral medication at screening. At week 24, the mean HbA_{1c} from baseline was reduced 0.74% and 0.99% for the one-step and two-step titration schedules, respectively. FPG was reduced by 10.1 mg/dL in the one-step titration group and 20.9 mg/dL in the two-step group.[18]

Lixisenatide Plus Metformin Versus Metformin Alone

In patients whose disease was insufficiently controlled on metformin alone, the GetGoal-M trial compared the addition of lixisenatide or placebo. Patients receiving lixisenatide were divided into two groups: once-daily morning injection and once-daily evening injection. The morning and evening lixisenatide injections reduced HbA_{1c} more than placebo by 0.5% and 0.4%, respectively ($P < 0.0001$ for both comparisons). The HbA_{1c} target of less than 7% was reached by significantly more patients receiving lixisenatide morning or evening injections (43% and 40.6%, respectively) compared with 22% of those receiving placebo ($P < 0.0001$). Patients in both lixisenatide groups saw a modest reduction in FPG from baseline compared with placebo (16.2 mg/dL and 10.8 mg/dL for the morning and evening, respectively) but experienced a more clinically significant reduction in the lowering of 2-h PPG to 81 mg/dL compared with placebo (measured only for the morning administration arm).[19]

The GetGoal-F1 trial studied the difference between one- and two-step dose increases of lixisenatide (similar to GetGoal-Mono) compared with placebo in a cohort of patients similar to those in GetGoal-M whose disease was insufficiently controlled on metformin alone. The results were comparable to those of the GetGoal-M trial (Table 2).[20]

Lixisenatide Versus Metformin With or Without Sulfonylurea

The GetGoal-M-Asia trial assessed the effect of adding lixisenatide 20 mcg to metformin with or without a sulfonylurea in patients living in China, Malaysia, Thailand, and Hong Kong. The trial used a one-step dose titration schedule. Compared with the control group, those receiving lixisenatide saw their HbA_{1c} decrease by 0.36% ($P = 0.0004$), FPG decrease by 8.7 mg/dL ($P = 0.0109$), and 2-h PPG decrease by 77.1 mg/dL ($P < 0.0001$). More patients achieved an HbA_{1c} of less than 7% with lixisenatide than with placebo (53% versus 38%; $P = 0.003$).[21]

Lixisenatide Versus Sulfonylurea With or Without Metformin

The GetGoal-S trial measured the effect on HbA_{1c} after adding once-daily lixisenatide for 24 weeks to the treatment of patients with diabetes inadequately controlled on a sulfonylurea with or without metformin. Approximately 85% of patients in both arms were taking a therapeutic dose of metformin. Compared with placebo, lixisenatide reduced HbA_{1c} by 0.74% more ($P < 0.0001$), reduced FPG by 11.4 mg/dL more ($P < 0.0001$), and reduced 2-h PPG by 107.7 mg/dL more ($P < 0.0001$). Compared with the control arm, considerably more patients in the lixisenatide arm achieved an HbA_{1c} of less than 7%. In addition, glycemic parameters such as 2-h PPG levels and fasting levels of glucagon, insulin, proinsulin, and C-peptide were significantly lower with lixisenatide than placebo.[22]

Lixisenatide Versus Pioglitazone With or Without Metformin

Lixisenatide significantly reduced HbA_{1c} in patients inadequately controlled on pioglitazone with or without metformin (more than 80% of patients were taking metformin) in the GetGoal-P trial, with a reduction of 0.56% over placebo ($P < 0.0001$). More patients receiving lixisenatide (52.3% and 28.9%) achieved the HbA_{1c} goal of less than 7% or less than 6.5%, respectively, compared to 26.4% and 10.1% of those taking placebo ($P < 0.0001$ for both). FPG was reduced by 15.14 mg/dL versus placebo ($P < 0.0001$).[23]

Lixisenatide Versus Established Basal Insulin Regimen

The GetGoal-L trial assessed the effect of adding lixisenatide 20 mcg to an established dose of basal insulin with or without metformin. On average, patients in GetGoal-L were taking 55 units of insulin daily. Compared with the control group, the lixisenatide group reduced HbA_{1c} by 0.4% ($P = 0.0002$) and 2-h PPG by 68.5 mg/dL ($P < 0.0001$), and significantly more patients achieved a goal HbA_{1c} of less than 7%. There was no significant difference in FPG between groups. By the end of the study, patients in the control group were using an average of 3.7 more units per day of insulin compared with the lixisenatide group ($P = 0.012$).[24]

The GetGoal-L-Asia trial, conducted in Japan, Republic of Korea, Taiwan, and the Philippines, assessed the addition of

lixisenatide to an established dose of basal insulin with or without a sulfonylurea (70% of patients were using a sulfonylurea). At baseline, patients were taking about 24 units of insulin per day. At study's end, the lixisenatide group achieved an average HbA_{1c} that was 0.88% lower than the control group ($P < 0.0001$). More patients in the lixisenatide group achieved an HbA_{1c} of less than 7% (35.6%) compared with the control group (5.2%). Significant differences were noted regarding FBG and 2-h PPG compared with the control group (Table 2).[25]

Lixisenatide Versus Newly Initiated Basal Insulin Regimen

Patients newly initiated on basal insulin who were unable to reach an HbA_{1c} target of less than 7% after 12 weeks of titrating to a target FPG range of 79.3–100.9 mg/dL were randomized to receive the addition of either lixisenatide 20 mcg once daily or placebo in the GetGoal-Duo-1 trial. Glycemic control was significantly improved in patients receiving lixisenatide, with an average HbA_{1c} reduction of 0.3% more than those in the placebo group ($P < 0.0001$). In addition, 56% of patients in the lixisenatide group were able to achieve the target HbA_{1c} goal of less than 7%, compared with 39% in the placebo group ($P = 0.0001$). Lixisenatide reduced 2-h PPG by an average of 57.6 mg/dL versus placebo ($P < 0.0001$). There was no significant difference in FPG between the groups. By the end of the study, patients in the control group were using an average of 2.2 more units per day of insulin compared with the lixisenatide group ($P = 0.03$).[26]

Lixisenatide Versus Exenatide Twice Daily

Lixisenatide 20 mcg once daily was compared with exenatide 10 mcg twice daily in GetGoal-X, a head-to-head, open-label, noninferiority trial. Lixisenatide lowered HbA_{1c} by an average of 0.79%, compared with a reduction of 0.96% for exenatide, resulting in a between-group difference of 0.17% (95% confidence interval [CI], 0.033–0.297). These results fell within the predefined noninferiority margin. Achievement of an HbA_{1c} target of less than 7% was similar between groups (48.5% with lixisenatide and 49.8% with exenatide), as was the reduction in FPG (21.9 mg/dL with lixisenatide and 26.1 mg/dL with exenatide).[27]

Body Weight

GLP-1 RAs have been known for promoting weight loss since December 2014, when a formulation of liraglutide gained Food and Drug Administration (FDA) approval for this indication.[28] GLP-1 RAs' effect on weight loss is thought to relate to their ability to directly and indirectly regulate appetite and promote satiety.[29] To assess the effect of lixisenatide on weight loss, weight was a secondary endpoint in the GetGoal program.

Of the four GetGoal studies that did not include concurrent use of a medication known to increase weight (such as insulin, a TZD, or a sulfonylurea), only the weight loss results of GetGoal-F1 achieved statistical significance (Table 2). In these studies, lixisenatide was associated with weight loss of 0.4 to 2.7 kg.[17–20]

Six trials within the GetGoal series involved the concurrent use of medications associated with weight gain. Collectively, weight changes in the lixisenatide group ranged from a 0.3-kg weight gain to a 1.8-kg weight loss. Only the results of GetGoal-S and GetGoal-L (which included use of a sulfonylurea and an established basal insulin dose, respectively) achieved statistical significance for a difference in weight loss between the two groups of 0.8 kg and 1.3 kg. In the GetGoal-Duo-1 trial, both groups gained weight, but patients in the lixisenatide arm gained less than those in the control arm (0.3 kg versus 1.2 kg, respectively; $P < 0.0012$).[21–26]

The GetGoal-X trial, which compared lixisenatide with twice-daily exenatide, resulted in weight loss of 2.96 kg and 3.98 kg, respectively. The between-group difference favored exenatide by 1.02 kg (95% CI, 0.456–1.581).[27]

ELIXA Trial

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial was a randomized, placebo-controlled, noninferiority study designed to meet a regulatory requirement by assessing the cardiovascular safety of lixisenatide in more than 6,000 patients with a recent acute coronary syndrome. Demographics were similar to most of the GetGoal trials. The primary endpoint was a composite of death from cardiovascular causes, nonfatal stroke, myocardial infarction, and unstable angina. The mean exposure to lixisenatide was 690 days per patient. Lixisenatide was found to be noninferior but not superior to placebo (adjusted hazard ratio, 1.02; 95% CI, 0.89–1.17). The frequency of each individual component of the primary endpoint was similar in both groups. These results were stable when further analysis was conducted adding additional cardiovascular endpoints such as hospitalization for heart failure and coronary revascularization procedures.[30]

DRUG INTERACTIONS

Through delayed gastric emptying, lixisenatide can decrease the rate of absorption of some medications. Caution is advised when using lixisenatide with medications that have a narrow therapeutic range, such as warfarin, or those that are concentration dependent, such as antibiotics. In addition, medications for which a delayed effect would be undesirable should be administered at least one hour before lixisenatide. Oral contraceptives should be taken either one hour prior to or 11 hours after lixisenatide administration.[14]

ADVERSE DRUG EVENTS

Overall, gastrointestinal side effects, including nausea, vomiting, and diarrhea, were the most commonly reported adverse events (Table 3). These effects appear to be dose dependent and often resolve within the first three to six weeks of lixisenatide therapy. Immunogenic effects have also been reported with this injectable medication. Patients could potentially develop antilixisenatide antibodies and exhibit a slightly higher incidence of allergic reactions and injection site reactions compared to antibody-negative patients. Antibody status is not routinely monitored; however, if patients experience worsening glycemic control or significant injection-site reactions, a different antidiabetic therapy should be considered.[14,31]

Throughout the GetGoal program, more patients experienced symptomatic hypoglycemia taking lixisenatide than those in the control groups. Hypoglycemia was more common in patients taking lixisenatide with an additional medication that is known to cause hypoglycemia. Of the more than 5,000 patients studied in GetGoal, six patients taking lixisenatide experienced severe hypoglycemia (defined as requiring assistance to correct due to neurological impairment).[17–27]

The adverse effect profiles of injectable GLP-1 RAs are fairly similar. In a 28-day study comparing several pharmaco-

Table 3 Most Common Adverse Events Reported in Select* GetGoal Trials[17–27]

Adverse Event	Lixisenatide	Placebo	Comparable GLP-1 RA
Nausea	25%	10%	35%
Vomiting	10%	2%	13%
Headache	8%	11%	NA
Diarrhea	10%	8%	13%
Dizziness	5%	2%	NA
Symptomatic hypoglycemia	9%	8%	8%

* Includes GetGoal-Mono, GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-P, GetGoal-X, GetGoal-L, and GetGoal-Duo1.

GLP-1 RA = glucagon-like peptide-1 receptor agonist; NA = not applicable.

dynamic measurements of lixisenatide with the GLP-1 RA liraglutide, patients treated with lixisenatide had a reported adverse event incidence of 58% compared with 73% for patients treated with liraglutide. When "decreased appetite" was excluded, the adverse event incidence decreased to 55% for lixisenatide and 65% for liraglutide.[32] When lixisenatide was compared with exenatide twice daily (GetGoal-X), fewer patients reported nausea in the lixisenatide group (24.5% versus 35.1%, respectively).[27]

WARNINGS AND PRECAUTIONS

Lixisenatide is contraindicated in patients with known hypersensitivity to lixisenatide or any of its inactive components. Lixisenatide has not been studied in patients with type-1 diabetes mellitus and should be avoided in this population. In addition, lixisenatide has not been evaluated in combination with DPP-4 inhibitors.

Unlike other GLP-1 agonists on the U.S. market, lixisenatide does not have a boxed warning. The FDA-approved prescribing information makes no mention or warning of the risk of thyroid C-cell tumors, including medullary thyroid carcinoma, or multiple endocrine neoplasia syndrome type 2.

In clinical trials, 21 cases of pancreatitis were reported in patients taking lixisenatide compared with 14 cases in control groups (an incidence rate of 21 versus 17 per 10,000 patient years, respectively). Of those who experienced pancreatitis while taking lixisenatide, three cases were reported as acute pancreatitis, five as chronic pancreatitis, and one as edematous pancreatitis. The remaining 12 cases were simply reported as pancreatitis. Observing patients for signs and symptoms of pancreatitis is recommended during lixisenatide therapy; should it occur, therapy should be discontinued and avoided thereafter. Clinicians should consider alternative therapies in patients with a history of pancreatitis.

Hypoglycemia is more likely if lixisenatide is used in addition to other medications that directly lower blood glucose. Due to the potential risk of hypoglycemia, dose reduction of sulfonylurea or basal insulin therapy may be necessary if lixisenatide is added to these regimens.

USE IN SPECIAL POPULATIONS

Pregnancy and Lactation

Limited information is available on the safety and efficacy of lixisenatide in pregnant women. In animal models, visceral closure and skeletal defects were observed in fetuses. Lixisenatide should be used during pregnancy only when the benefits outweigh the potential risks to the fetus.

The presence of lixisenatide in milk, effects on the infant, and effects on milk production have not been studied in humans. However, in lactating rats, 9.4% of lixisenatide and its metabolites passed into milk. Benefits of breastfeeding to the infant and the benefit of lixisenatide to the mother should be considered along with the potential harm to the infant.[33–35]

Geriatric and Pediatric Patients

In adults 65 years and older, no apparent differences were observed compared with the general population.[36] This was confirmed with the publication of the GetGoal-O trial, which found results similar to the general population in a patient population that was 70 years of age or older on a combination of antidiabetic agents, including insulin.[37] This medication has not been studied in pediatric patients.

Renal Impairment

No dosage adjustment is required for mild-to-moderate renal impairment (estimated glomerular filtration rate [eGFR] of 60–89 mL/min/1.73 m^2 and eGFR of 30–60 mL/min/1.73 m^2, respectively). However, additional monitoring is recommended for these patients because they could be at increased risk of adverse events, including dehydration, that could worsen their renal function. Patients with severe renal impairment (eGFR of 15–30 mL/min/1.73 m^2) should be monitored closely for increased risk of adverse events, particularly gastrointestinal-related events, and for worsening renal function. Lixisenatide has not been studied in patients with end-stage renal disease.[14]

Hepatic Impairment

No studies have evaluated lixisenatide in patients with acute or chronic hepatic dysfunction, as most lixisenatide is removed by the kidneys. However, hepatic impairment is unlikely to affect the pharmacokinetic profile of lixisenatide.[14]

DOSAGE AND ADMINISTRATION

Patients who are prescribed lixisenatide are instructed to follow a one-step dose increase schedule. Initially patients should take 10 mcg administered subcutaneously once daily for 14 days using the green prefilled starter pen containing 14 preset doses. The dose should then be increased to a once-daily maintenance dose of 20 mcg starting on day 15 using the burgundy prefilled maintenance pen containing 14 preset doses. This medication should be given within one hour before patients' first meal of the day.[14]

Prior to the initial dose of either the starter or maintenance lixisenatide pens being administered, patients will need to activate each pen once in a manner not too dissimilar to use of a Victoza (liraglutide) pen. Also, similar to liraglutide and most insulin pens, lixisenatide pens not in use should be refrigerated while pens currently in use can stay at room temperature.[14]

COST

Lixisenatide is currently available in the U.S. as Adlyxin. When initiating treatment, prescribers should first write for

the Adlyxin starter pack, which contains one green starter pen (50 mcg/mL; 3 mL each) and one burgundy maintenance pen (100 mcg/mL; 3 mL each). Afterward, prescriptions should be written for the Adlyxin maintenance pack, which contains two burgundy maintenance pens.[14] It is important to note that both prescriptions provide the patient with a 28-day supply. The starter pack and the maintenance pack have the same average wholesale price of $669.[38] The manufacturer recommends that Adlyxin pens be used with pen needles from Becton Dickinson, Ypsomed, or Owen Mumford that are shorter than 8 mm.[14]

P&T COMMITTEE CONSIDERATIONS

The American Association of Clinical Endocrinologists (AACE) glycemic control algorithm published in 2015 suggests using GLP-1 agonists as a first-line therapy option in treating T2DM with an HbA_{1c} of 7.5% or less, second only to metformin as a monotherapy option. The 2016 AACE guidelines also state that GLP-1 agonists have the strongest recommendation for use as a second or third agent in combination with metformin or other first-line options for patients with an HbA_{1c} of 7.5% or greater. GLP-1 agonists, along with DPP-4 inhibitors, have largely replaced sulfonylureas and glinides as second-line therapy options due to their overall efficacy and safety profiles. The ADA suggests using any one of six treatment options, including GLP-1 agonists, for patients who have not achieved an HbA_{1c} of 7.5% or less after three months of treatment with metformin and lifestyle changes.

There are several points to consider when comparing lixisenatide to other GLP-1 agonists. Lixisenatide has not been shown to reduce the risk of major adverse cardiovascular events in patients with established cardiovascular disease (unlike liraglutide). Compared with some other GLP-1 agonists (liraglutide, dulaglutide, albiglutide, and once-weekly exenatide), lixisenatide does not have any boxed warnings in its labeling regarding thyroid C-cell tumors, including medullary thyroid carcinoma.

Lixisenatide should be administered with the first meal of the day, whereas liraglutide can be administered regardless of meals, and twice-daily exenatide is administered with the morning and evening meal. Lixisenatide is likely to be easier to administer compared to certain once-weekly GLP-1 agonists that have pen devices that are designed to mix medication into a solution (albiglutide and once-weekly exenatide), but not likely easier to administer than once-weekly dulaglutide. If patients prefer daily administration but have difficulty with the dial mechanism of liraglutide pens, they should find the preset dose of lixisenatide a bit easier. Patients will need to be counseled to take care to utilize the correct pen when being prescribed the Adlyxin starter pack. Similar to the once-weekly GLP-1 agonists, both the starter and maintenance packs are considered to be 28-day supplies.

Given that there are no major, obvious differences in tolerability, efficacy on glycemic parameters, weight loss, or overt advantages regarding administration, it is likely that use of lixisenatide, in place of other GLP-1 agonists will be based on cost (to the patient, health system, and payer).

CONCLUSION

Lixisenatide is the latest once-daily GLP-1 agonist approved for treating patients with type-2 diabetes. Studies show that lixisenatide significantly reduces HbA_{1c} by 0.5–1%, reduces fasting plasma glucose and postprandial glucose, and is associated with modest reductions in body weight. Patients treated with lixisenatide experienced hypoglycemia more often than patients not treated with a GLP-1 agonist, but these occurrences were not severe and rarely led to discontinuation of therapy. Lixisenatide was shown to be noninferior to exenatide administered twice daily in regard to lowering HbA_{1c} and trended toward being better tolerated.

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