

Lixisenatide—Once-daily Glucagon-like Peptide-1 Receptor Agonist in the Management of Type 2 Diabetes

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Abstract

The glucagon-like peptide-1 receptor agonist diabetes medications have become important due to their unique features, such as their potency of glycosylated hemoglobin (HbA_{1c}) lowering, durability of effect, glucose-dependent insulin secretion resulting in a low risk of hypoglycemia, glucagon suppression, and weight loss. Lixisenatide is an investigational compound in this class, exhibits all of these features, and has some unique properties, which are highlighted in this review. The pharmacology of lixisenatide, the results of recent clinical trials investigating this agent, and its potential role in the management of type 2 diabetes will be discussed.

Keywords

Lixisenatide, glucagon-like peptide-1 receptor agonist, type 2 diabetes

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Type 2 diabetes is a progressive disease of the beta cells characterized by declining insulin secretion and varying degrees of insulin resistance resulting in hyperglycemia. It is a chronic progressive disease of increasing incidence. In the USA, 25.6 million people aged over 20 years have type 2 diabetes¹ and the prevalence is projected to increase to 36 million people in the next 20 years.² This trend follows that of the obesity epidemic. Patients with type 2 diabetes are at increased risk of microvascular and macrovascular complications (neuropathy, renal disease, retinopathy, myocardial infarction, cerebrovascular accident, peripheral vascular disease). Most patients need lifestyle changes and polypharmacy to control hyperglycemia.

The American Association of Clinical Endocrinologists and American Diabetes Association guidelines recommend lifestyle changes and metformin as first-line therapy.^{3,4} The glucagon-like peptide-1 (GLP-1) receptor agonist class of medications may be used, typically as part of combination therapy, and may have certain advantages over older medications. GLP-1 receptor agonists stimulate insulin secretion in a glucose-dependent manner (thus having a low risk of hypoglycemia), suppress glucagon secretion, improve beta cell function, slow down gastric emptying, and promote early satiety and consequent weight loss.^{5,6} In addition, GLP-1 agonists have potential cardiovascular benefits with weight reduction, improvements in lipid profile and blood pressure, and decreased markers for cardiovascular risk and inflammation (including C-reactive protein).⁷ GLP-1 receptor agonists approved by the US Food and Drug Administration are twice-daily exenatide (Byetta®; Amylin

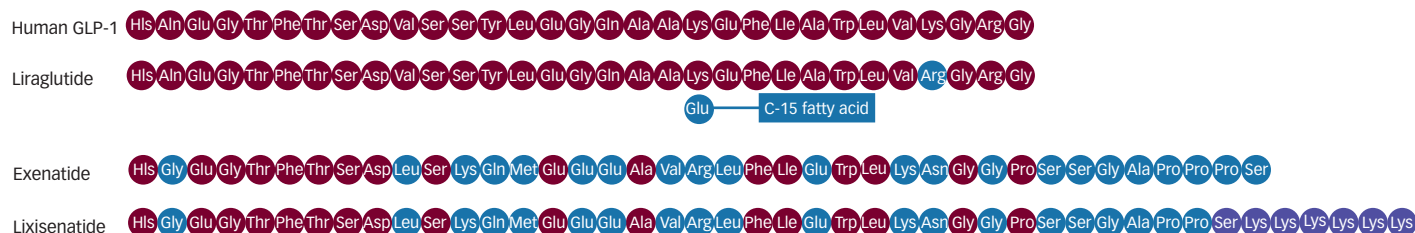
Pharmaceuticals, Inc. and Lilly USA, LLC) and once-daily liraglutide (Victoza®; Novo Nordisk). This article reviews lixisenatide (Lyxumia®, AVE0010, ZP10), an investigational once-daily GLP-1 receptor agonist in phase III development for the treatment of type 2 diabetes, which is being developed by Sanofi-aventis under license from Zealand Pharma A/S.⁸

Pharmacology

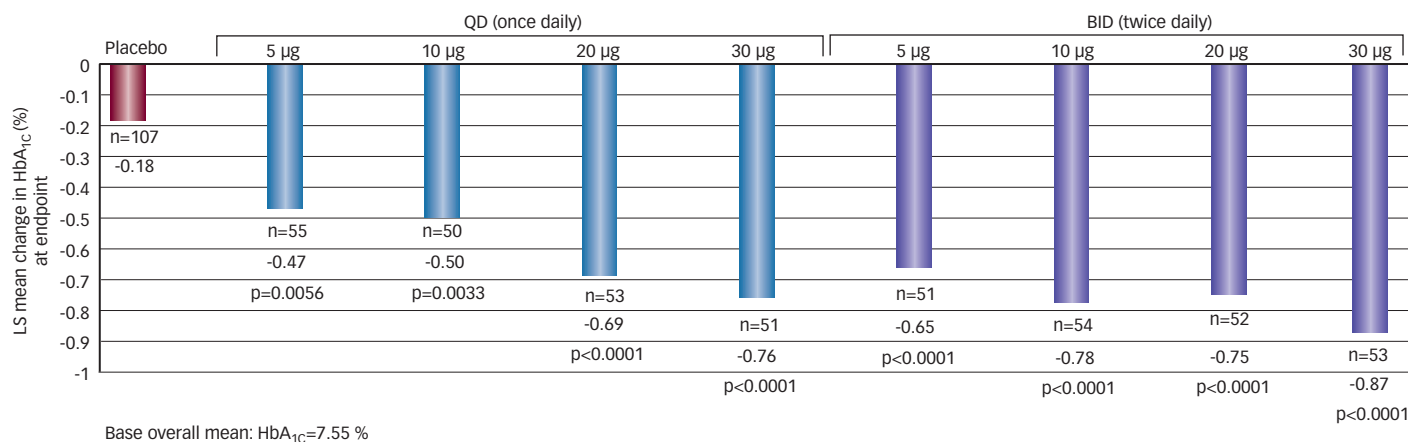
Lixisenatide is a 44-amino-acid peptide based on exendin-4⁹ and modified to avoid rapid degradation by dipeptidyl peptidase-IV.¹⁰ The modification consists of the deletion of one proline residue and addition of six lysine residues at the C-terminal.¹¹ While the affinity of exendin-4 for the GLP-1 receptor is similar to that of human GLP-1,⁹ the affinity of lixisenatide for the GLP-1 receptor is four times greater than that of human GLP-1^{9,12} (see *Figure 1* and *Table 1*). Lixisenatide is also highly selective for the GLP-1 receptor.¹³ Pharmacokinetics studies show that maximum lixisenatide plasma concentration (C_{max}) of 84 pg/ml is seen two hours (t_{max}) after the subcutaneous injection of lixisenatide 20 µg.¹⁴ The half-life (t_{1/2}) is 2.6 ± 1 hours.¹⁵ Lixisenatide is filtered in the glomerulus and degraded in the renal tubules.¹⁵ Pharmacokinetic parameters for lixisenatide and the other GLP-1 receptor agonists are shown in *Table 1*.

Preclinical Studies

In a study using rat insulinoma cell line INS-1, lixisenatide protected B-cells against fatty acid and cytokine-induced apoptosis^{9,16} and inhibition of cytokine-induced apoptosis was significantly greater with

Figure 1: Structure of the Glucagon-like Peptide-1 Receptor Agonists Liraglutide, Exenatide, and Lixisenatide

The amino acid sequence of three glucagon-like peptide-1 (GLP-1) receptor agonists are shown in comparison to the sequence of human GLP-1; differences with human GLP-1 are indicated by blue circles; differences between exenatide and lixisenatide are shown by purple circles. Sources: data taken from Werner, et al., 2010⁸ and Nauck, 2011² with permission.

Figure 2: Dose-dependent Effects of Lixisenatide On Glycosylated Hemoglobin In Phase II Clinical Trial

HbA_{1c} = glycosylated hemoglobin; LS = least squares. No significant differences were seen between once daily and twice daily dosing. Source: adapted from Ratner RE, et al., 2010¹⁴ with permission.

lixisenatide and exendin-4 than with human GLP-1. Moreover, the combination of insulin glargine with lixisenatide or exendin-4 significantly reduced apoptosis compared with each agent alone.¹⁶

The insulin secretion pattern was studied in isolated pancreas from male Zucker diabetic fatty (ZDF) rats treated with lixisenatide and compared with isolated pancreas from lean and obese ZDF rats not treated with lixisenatide.¹⁷ Biphasic insulin secretion was preserved in the lixisenatide-treated obese ZDF rats, similar to what happened in lean controls, but was absent in older obese ZDF rats.¹⁷ In a study using human islet cells, lixisenatide showed dose-dependent improvement of glucose-stimulated insulin secretion.¹⁸

Improvement of oral glucose tolerance with lixisenatide was shown in animal studies (obese ZDF rats, db/db mice, and dogs).^{12,19,20} Decreased post-prandial glucose excursion following a mixed meal was seen in mongrel dogs.²¹ Marked reductions in glucose levels^{12,19,20} and glycosylated hemoglobin (HbA_{1c})¹⁹ were shown in lixisenatide-treated animals compared with saline-treated animals.

In a comparison study of dogs treated with lixisenatide or liraglutide, blood glucose excursion following glucose challenge in oral glucose tolerance tests was significantly lower in dogs treated with lixisenatide. A similar effect was seen in C57BL/6J mice following a liquid meal.²² Starting at different doses, both lixisenatide (1 µg/kg) and liraglutide

Table 1: Pharmacokinetics of Available Glucagon-like Peptide-1 Receptor Agonists

GLP-1 Receptor Agonist	t _{1/2}	GLP-1 Receptor Affinity	Dosing Frequency
Human GLP-1	~1-2 minutes ³¹	--	--
Exenatide	~2.4 hours ³²	~1x ⁹	Twice daily ³³
Liraglutide	~13 hours ³²	~1x ³⁴	Once daily ³⁵
Exenatide LAR	~2 weeks ³⁶	~1x ⁹	Once weekly ³⁶
Lixisenatide	~2.6 hours ³⁷	~4x ⁹	Once daily ²⁴

GLP-1 = glucagon-like peptide-1; LAR = long-acting release.

(≥500 µg/kg) inhibited gastric emptying in Wistar rats.²²

Lixisenatide was shown to be cardioprotective in a study on isolated Langendorff-perfused rat hearts in which the left anterior descending coronary artery was transiently occluded for 45 minutes and then reperfused for 120 minutes. There was significant reduction in the infarct size with lixisenatide compared with vehicle control.²³

Phase II Studies

A dose-finding study was undertaken in patients with type 2 diabetes not controlled by metformin. This was a multinational, 13-week, randomized, double-blind, parallel-group, placebo-controlled study that enrolled 542 patients inadequately controlled after at least three months of metformin therapy.²⁴ Participants had a mean age of 56 ± 9 years with

Table 2: Overview of Phase III Clinical Trials of Lixisenatide

Study Description	Trial Registration No.	No. Subjects	Completion Date	Results
<i>GetGoal-Mono</i> Efficacy and safety of lixisenatide as monotherapy in patients with type 2 diabetes ²⁷	NCT00688701 ³⁸	361	December 2009	Significant decrease in HbA _{1c} , 2hr-PPG, and FPG; significant number of patients achieving HbA _{1c} <7 % and <6.5 %
<i>GetGoal-L-Asia</i> Efficacy and safety of lixisenatide as add-on to basal insulin with or without sulfonylurea versus placebo ²⁸	NCT00866658 ³⁹	311	June 2010	Significant decrease in HbA _{1c} , 2hr-PPG, glucose excursion, average 7-point SMPG; significant number of patients achieving HbA _{1c} <7 % and <6.5 %
<i>GetGoal-X</i> Effect of lixisenatide versus exenatide on glycemic control in patients with type 2 diabetes insufficiently controlled on metformin ²⁹	NCT00707031 ⁴⁰	634	November 2010	Lixisenatide had similar HbA _{1c} lowering and weight loss effects as exenatide
<i>GetGoal-S</i> Effect on glycemic control of lixisenatide as add-on to sulfonylurea with or without metformin versus placebo ³⁰	NCT00713830 ⁴¹	859	January 2011	Significant reduction in HbA _{1c} , improvement in 2hr-PPG and FPG, and decrease in body weight
<i>GetGoal-L</i> Efficacy and safety of lixisenatide as add-on to basal insulin with or without metformin versus placebo ²⁶	NCT00715624 ⁴²	495	February 2011	Significant reduction in HbA _{1c} , improvement in PPG, and decrease in body weight
<i>GetGoal-M</i> Effect on glycemic control of lixisenatide (morning versus evening dose) as add-on to metformin compared with placebo ⁵¹	NCT00712673 ⁴³	680	March 2011	Both morning and evening lixisenatide dosing improved glycemic control when added to metformin
<i>GetGoal-F1</i> Effect on glycemic control of lixisenatide in two titration regimens as add-on to metformin versus placebo ⁵²	NCT00763451 ⁴⁵	450	January 2011	Both 1-step and 2-step titration regimens were effective and well-tolerated
<i>GetGoal-P</i> Glycemic control of lixisenatide as add-on to pioglitazone versus placebo	NCT00763815 ⁴⁶	450	June 2011	Not available
<i>GetGoal-Mono-Japan</i> Efficacy and safety of lixisenatide as monotherapy in patients with type 2 diabetes	NCT00905255 ⁴⁷	66	January 2011	Not available
Lixisenatide versus sitagliptin as add-on to metformin in patients with type 2 diabetes, evaluating effects on glycemic control and body weight in 24 weeks	NCT00976937 ⁴⁸	~300	April 2011	Not available
Lixisenatide as add-on to metformin and insulin glargine in patients with type 2 diabetes compared with placebo, evaluating effects on glycemic control in 24 weeks ⁵³	NCT00975286 ⁴⁹	~450	September 2011	The combination of basal insulin and lixisenatide reduced HbA _{1c} and significantly improved 2hr-PPG
<i>ELIXA</i> Evaluate cardiovascular outcomes of lixisenatide in patients with type 2 diabetes who had a recent acute coronary syndrome compared with placebo	NCT01147250 ⁵⁰	~6,000	October 2013	Ongoing study
<i>GetGoal-M-As</i> Efficacy of lixisenatide as add-on to metformin with or without sulfonylurea versus placebo in reducing HbA _{1c} in a period of 24 weeks	NCT01169779 ⁴⁴	~380	December 2011	Ongoing study

2hr-PPG = two-hour post-prandial glucose; FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; SMPG = self-monitoring of plasma glucose.

mean disease duration of 6.6 ± 5 years, mean body mass index (BMI) of 31.9 ± 4 kg/m², and mean baseline HbA_{1c} of 7.5 ± 0.6 %. Participants were randomized to one of 12 groups: lixisenatide (5, 10, 20 or 30 µg) administered once or twice daily or four volume-matched placebo treatments administered twice daily. All lixisenatide groups experienced dose-dependent reductions in HbA_{1c} ranging from 0.47 % to 0.76 % in the once-daily regimen and from 0.65 % to 0.87 % in the twice-daily regimen compared with placebo (see *Figure 2*).²⁴

Secondary efficacy endpoints were the percentage of patients achieving HbA_{1c} of <7 % and <6.5 %, changes in body weight,

fasting plasma glucose, and two-hour post-prandial plasma glucose following a standardized breakfast. By the end of the study (week 13), significantly higher proportions of patients achieved HbA_{1c} <7 % in lixisenatide-treated groups (47–69 % in once-daily and 51–77 % in twice-daily groups) compared with the placebo group (32 %). A dose-dependent reduction in body weight was seen in lixisenatide-treated patients, which was significant in the 20 µg once-daily (-3.01 ± 0.41 kg), 30 µg once-daily (-3.47 ± 0.41 kg), and 30 µg twice-daily (-3.89 ± 0.41 kg) groups compared with placebo (-1.94 ± 0.32 kg).²⁴ Significant reductions in fasting plasma glucose were observed in the 30 µg once-daily (-23.76 ± 4.50 mg/dl), 10 µg

twice daily (-17.64 ± 4.32 mg/dl), 20 μ g twice-daily (-20.34 ± 4.50 mg/dl), and 30 μ g twice-daily (-25.56 ± 4.50 mg/dl) groups compared with placebo (-3.78 ± 3.42 mg/dl).²⁴ Mean two-hour post-prandial glucose concentrations in all lixisenatide groups showed a significant reduction by comparison with placebo.²⁴

The study indicated that efficacy was similar between the once- and twice-daily regimens and that there was a dose–response relationship. A dose of 20 μ g lixisenatide once daily demonstrated the best efficacy:tolerability ratio. The data suggest further increases in the dose may not provide added benefit.

In a phase II randomized, double-blind, placebo-controlled study involving 64 patients, lixisenatide once or twice daily was added to metformin and/or a sulfonylurea for 28 days. The study measured the effects of lixisenatide on post-prandial change in blood glucose following a standardized breakfast and on levels of fasting and mean plasma glucose and HbA_{1c}. It also evaluated the safety and tolerability of the drug.²⁵ The lixisenatide dose started at 5 μ g subcutaneous once daily or twice daily and was increased by 2.5 μ g every five days to a maximum dose of 20 μ g. On day 28, post-prandial blood glucose levels following a standardized breakfast, as well as mean plasma glucose and HbA_{1c} levels, were significantly reduced in both the once-daily and twice-daily lixisenatide 20 μ g groups compared with placebo.²⁵

Phase III Clinical Trial Program

The GetGoal clinical trial program initially consisted of nine phase III trials evaluating the efficacy and safety of lixisenatide in the treatment of patients with type 2 diabetes as monotherapy or in combination with different oral antidiabetes agents and/or insulin. Additional studies have been added to the GetGoal clinical program, including randomized studies comparing lixisenatide to sitagliptin and a large clinical trial evaluating cardiovascular outcomes with lixisenatide in a type 2 diabetes patient who had had a recent acute coronary syndrome. The trials began in May 2008 and 4,300 patients have been enrolled in total.²⁶ At the time of writing, the results of some of these trials have been made available as press releases, or have been presented at scientific meetings and published in abstract form. *Table 2* shows a summary of the clinical trial program.

GetGoal-Mono

GetGoal-Mono was a 12-week, double-blind, randomized controlled trial that assessed the efficacy and safety of lixisenatide as monotherapy for type 2 diabetes.²⁷ A total of 361 type 2 diabetes patients not on any diabetes medication were randomized to one of four groups: lixisenatide two-step titration (10 μ g once daily for one week, followed by 15 μ g once daily for one week, and 20 μ g once daily thereafter; n=120), lixisenatide one-step titration (10 μ g once daily for two weeks, and 20 μ g once daily thereafter; n=119), placebo two-step titration (n=61), or placebo one-step titration (n=61). Patients had a mean age of 54 years, mean disease duration of 2.5 years, and HbA_{1c} in the range 7–10 %.

In the lixisenatide groups, HbA_{1c} decreased significantly ($p < 0.0001$) by comparison with placebo (lixisenatide two-step group -0.73 ± 0.12 %; lixisenatide one-step group -0.85 ± 0.12 %; placebo -0.19 ± 0.12 %). At the end of the study, the lixisenatide groups included significantly

Table 3: Additional Results for Lixisenatide versus Placebo from the GetGoal-L-Asia Study²⁸

	Lixisenatide	Placebo	LS Mean Difference (95 % CI)
Two-hour post-prandial glucose levels (mg/dl)	-143.28 ± 10.73	-2.52 ± 10.49	-140.94 (-159.966 to -121.842)
Glucose excursion (mg/dl)	-127.62 ± 10.37	2.52 ± 9.76	-129.96 (-148.41 to -111.672)
Average 7-point self-monitoring of plasma glucose (mg/dl)	34.38 ± 4.90	10.08 ± 4.88	-24.3 (-33.174 to -15.498)

CI = confidence interval; LS = least squares.

more patients with HbA_{1c} ≤ 6.5 % (lixisenatide two-step group 31.9 %; lixisenatide one-step group 25.4 %; placebo 12.5 %) and HbA_{1c} < 7.0 % (lixisenatide two-step group 52.2 %; lixisenatide one-step group 46.5108 %; placebo 26.8108 %). They also had significantly higher reductions in two-hour post-prandial glucose levels (lixisenatide two-step group -81.18 ± 4.56 mg/dl; lixisenatide one-step group -98.46 ± 9.9 mg/dl; placebo -11.7 ± 10.08 mg/dl) and fasting plasma glucose levels (lixisenatide two-step group -12.24 ± 4.5 mg/dl; lixisenatide one-step group -16.02 ± 4.5 mg/dl; placebo 3.42 ± 4.68 mg/dl).²⁷

GetGoal-L-Asia

GetGoal-L-Asia was a 24-week multicenter, randomized, double-blind, placebo-controlled clinical trial that evaluated the efficacy and safety of lixisenatide 20 μ g once daily in 311 patients with type 2 diabetes (mean age 58 years, disease duration 14 years, and BMI 25 kg/m²) from Japan, South Korea, Taiwan, and the Philippines who were inadequately controlled with basal insulin and/or a sulfonylurea.²⁸

At week 24, lixisenatide had significantly reduced mean HbA_{1c} levels from baseline (-0.77 ± 0.137 %) compared with placebo (0.11 ± 0.131 %; least squares [LS] mean difference -0.88 [95 % CI -1.116 to 0.650]). The percentages of patients on lixisenatide who achieved HbA_{1c} < 6.5 % and < 7 % were 17.8 % and 35.6 %, respectively, compared with 1.3 % and 5.2 %, respectively, in the placebo group ($p < 0.0001$).²⁸ Other measures of efficacy also were significantly improved (see *Table 3*).²⁸

GetGoal-X

GetGoal-X compared lixisenatide to exenatide in a 24-week multicenter, randomized, open-label, parallel-group study of 634 type 2 diabetes patients insufficiently controlled on metformin.²⁹ The patients had a mean age of 57.4 years, a disease duration of 6.8 years, a BMI of 33.6 kg/m², and HbA_{1c} levels of 8 %. The decrease in HbA_{1c} with lixisenatide (-0.79 ± 0.05 %) was comparable with that seen with exenatide (-0.96 ± 0.05 %; LS mean difference 0.17 [95 % CI 0.03–0.30]; $p = 0.17$). Similar percentages of patients achieved HbA_{1c} < 7 % with lixisenatide (48.5 %) and with exenatide (49.8 %). The mean decrease in body weight was comparable between the lixisenatide and exenatide groups.²⁹

GetGoal-S

GetGoal-S, a 24-week randomized, double-blind, placebo-controlled clinical study, evaluated the efficacy and safety of lixisenatide in type 2 diabetes patients insufficiently controlled on sulfonylurea and/or

metformin. In the study, 859 patients were randomized to either lixisenatide or placebo.³⁰ Doses were increased in a step-wise manner to 20 µg once daily in both groups.

As an add-on therapy to sulfonylurea with or without metformin, lixisenatide significantly reduced HbA_{1C} levels and improved two-hour post-prandial glucose and fasting plasma glucose levels compared with placebo.³⁰ Moreover, patients on lixisenatide experienced a significant decrease in body weight compared with those on placebo.³⁰ At 24 weeks, lixisenatide significantly reduced HbA_{1C} compared with placebo (-0.85 versus -0.10%; $p < 0.0001$). Lixisenatide also significantly improved two-hour PPG (after a standardized meal test) (-6.19 versus -0.21 mmol/l), FPG (-0.99 versus -0.36 mmol/l), and body weight (-1.76 versus -0.93 kg) and increased the proportion of patients achieving HbA_{1C} <7.0 % (36.4 versus 13.5 %) ($p < 0.0001$).

GetGoal-L

GetGoal-L is another 24-week clinical study in which 495 patients were randomized either to lixisenatide or placebo in addition to basal insulin with or without metformin. Compared with placebo, lixisenatide significantly decreased mean HbA_{1C} ($p = 0.0002$), improved post-prandial glucose following a standardized meal ($p < 0.0001$), and reduced mean body weight ($p < 0.0001$).

Adverse Effects

Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions to lixisenatide were frequently observed in clinical trials. Nausea was the most frequent event—the incidence ranged from 20 % to 40 % in the lixisenatide arm compared with 4–5 % in the placebo arm^{24, 26–29}—but it was transient and dose-dependent.

Other reported gastrointestinal reactions included vomiting, diarrhea, constipation, dyspepsia, abdominal distension, and abdominal pain.¹¹ In the GetGoal-X study, nausea was experienced less frequently with lixisenatide 20 µg once daily (24.5%) than with exenatide 10 µg twice daily (35.1 %) [$p < 0.05$].²⁹ Incidences of diarrhea (10.4% and 13.3 %) and vomiting (10.1 % and 13.3 %) in the lixisenatide and exenatide groups, respectively, were also similar.²⁹

Hypoglycemia

Symptomatic hypoglycemia has been reported with lixisenatide as monotherapy²⁷ and in combination with other diabetes agents²⁴ and/or insulin.²⁸ No case of severe hypoglycemia has been reported.^{24, 28, 29} Symptomatic hypoglycemia was reported in more patients on lixisenatide 20 µg once daily added to basal insulin and/or sulfonylurea (42.9 %) than in patients on placebo (23.6 %).²⁸

The rate of symptomatic hypoglycemia in the lixisenatide group was reduced if patients taking a sulfonylurea were excluded (lixisenatide 31.8 %; placebo 28.3 %).²⁸ The risk of symptomatic hypoglycemia was not significantly increased with lixisenatide 20 µg once daily as an add-on to sulfonylurea with or without metformin compared to placebo at week 24.³⁰ In the GetGoal-X study, patients taking lixisenatide had six-fold fewer hypoglycemic events and three-fold fewer instances of symptomatic hypoglycemia (2.5 %) than patients taking exenatide (7.9 %) [$p < 0.05$].²⁹

Antibodies to Lixisenatide

It is postulated that antibody formation may decrease the effect of GLP-1 agonists on glucose control.¹¹ The rate of antibody formation in patients treated with lixisenatide ranged from 43.1 % with lixisenatide 10 µg once daily to 71.2 % with lixisenatide 20 µg twice daily;²⁴ however, no differences were observed in the efficacy and safety profile of lixisenatide when given to patients with or without antibodies.²⁴

Other Reported Adverse Effects

Reported rates of dizziness and headache with lixisenatide are similar to those reported in placebo groups.²⁴ One patient taking lixisenatide 30 µg once daily experienced loss of consciousness of a few seconds' duration, which led to withdrawal from the study.²⁴ One patient taking lixisenatide 10 µg once daily discontinued the medication three weeks into the study following two separate allergic reactions 10 minutes after receiving the drug; on the first occasion, the patient developed pruritus, and three days later the patient had swollen lips and tongue and difficulty breathing. The events were resolved with an oral antihistamine.²⁴ Two cases of urticaria occurred with lixisenatide (compared to three with placebo).²⁴

Potential Role of Lixisenatide Among Glucagon-like Peptide-1 Receptor Agonist Medications

The first incretin-based therapy, exenatide, was launched in 2005. The novel mechanisms of action of GLP-1 agonists and their multiple associated benefits make them desirable options for the treatment of type 2 diabetes. The second incretin-based therapy to be approved, liraglutide, overcame some of the disadvantages of exenatide, including the need for multiple daily injections timed with meals and a relatively high incidence of nausea. Once-weekly exenatide (Bydureon®; Amylin Pharmaceuticals, Inc., Lilly USA, LLC, and Alkermes, Inc.) has been approved for use in Europe and is currently under review by the US Food and Drug Administration. Once-weekly administration will appeal to many patients, although the delivery system may not be as simple or as comfortable as those of the shorter-acting medications in this class. Medical providers will be able to offer patients the choice between the convenience of the once-weekly injection and the simplicity of the once-daily devices.

Review of the available data suggests that lixisenatide will be effective as a once-daily GLP-1 receptor agonist. Although it has a short half-life, similar to that of exenatide, its biological effects appear prolonged, perhaps due its higher affinity to the GLP-1 receptor. Once-daily administration of lixisenatide and twice-daily administration of exenatide achieved similar lowering of HbA_{1C} levels in the GetGoal-X study.²⁹

Lixisenatide has not been compared with liraglutide, the other once-daily GLP-1 agonist. Because liraglutide has a substantially longer half-life, it may reduce fasting plasma glucose more effectively than lixisenatide; however, potential slowing of gastric emptying with lixisenatide may result in greater improvements in post-prandial glucose levels. Additional clinical trials are required to confirm this. Data from further clinical trials and post-approval clinical experience will help clinicians decide how well lixisenatide compares with the other GLP-1 agonists. ■

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