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New Drug Evaluation: lixisenatide injection, subcutaneous

Date of Review: January 2017
Generic Name: lixisenatide
PDL Class: GLP-1 receptor agonists

End Date of Literature Search:
Brand Name (Manufacturer): Adlyxin (Sanofi-Aventis)
AMCP Dossier Received: Yes

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:

- Is there evidence that lixisenatide improves outcomes versus other GLP-1 receptor agonists in patients with type 2 diabetes mellitus (T2DM), including hemoglobin A1c (A1C) reduction, microvascular and macrovascular outcomes and mortality?
- Is there evidence that lixisenatide is safer than other GLP-1 receptor agonists in patients with T2DM?
- Are there subpopulations of patients with T2DM for which lixisenatide may be more effective or associated with less harm?

Conclusions:

- Lixisenatide approval was based on 11 phase 3 clinical trials.[1-11] Eight trials were placebo-controlled and 3 were active treatment comparisons to either sitagliptin, exenatide or insulin glulisine. All trials were designed and funded by the manufacture Sanofi-Aventis. Limitations to the data include short trial durations (12-26 weeks for most) and insufficient evidence for improvement in any health outcomes. The studies are most applicable to patients with moderately uncontrolled T2DM (HbA1c around 8%) with few comorbidities.
- There is insufficient evidence to determine if lixisenatide has any effect on microvascular outcomes.
- One study provides moderate strength evidence that lixisenatide is not associated with increased risk for macrovascular outcomes compared to placebo. Occurrence of the composite endpoint of cardiovascular mortality, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for unstable angina was 13.4% in the lixisenatide group and 13.2% in the placebo group (HR 1.02; 95% CI, 0.89 to 1.17).[11] Most events were nonfatal MIs (61.9% in the placebo group and 62.8% in the lixisenatide group). A predefined secondary endpoint of all-cause mortality found no statistically significant difference between lixisenatide and placebo (7.0% and 7.4%, respectively; p=0.50).
- There is moderate quality evidence that lixisenatide lowered A1c by -0.3% to -0.75% more than placebo as monotherapy, in combination with metformin, or in combination with metformin and basal insulin, sulfonylurea, or thiazolidinedione in patients with a mean age of 56 years and baseline A1c of 8.1%.[1-7] The number of patients who obtained an A1c less than 7% was more common in patients treated with lixisenatide than placebo (number-needed-to-treat [NNT] of 4-6.[1-7]

- In patients with moderately uncontrolled T2DM (mean A1c of 8.02%) and 7-year history of a diabetes diagnosis, lixisenatide was noninferior to exenatide at lowering A1c based on moderate evidence.[8] Hemoglobin A1c decreased -0.79% with lixisenatide compared to -0.96% with exenatide (LSMD 0.17%; 95% CI, -0.033 to 0.297%). All patients were on metformin. A similar number of patients in each group obtained an A1c less than 7%.[8]
- There is low quality evidence that lixisenatide is not superior to sitagliptin, a DPP-4 inhibitor, based on the composite endpoint of the number of patients who obtained an A1c less than 7% and who achieved weight loss of 5% or more, based on one small study with high risk of bias.[9]
- There is low quality evidence lixisenatide is noninferior to the rapid-acting insulin glulisine (with background insulin glargine ± metformin in both groups) at reducing A1c in patients with a 12-year history of T2DM and moderately uncontrolled glucose (mean A1c 8.5%).[10] Lixisenatide and insulin glulisine given once daily both resulted in A1c lowering of -0.6% compared to -0.8% for insulin glulisine given three times a day. The difference between lixisenatide and insulin glulisine once daily was -0.1% (95% CI, -0.17 to 0.06%) and -0.2% (95% CI, 0.10 to 0.33%) for lixisenatide compared to three times daily insulin glulisine. The number of patients obtaining an A1c less than 7% were similar for lixisenatide, once daily insulin glulisine and three times daily insulin glulisine (42.1%, 38.4% and 49.2%, respectively).[10]
- Common adverse events seen with GLP-1 receptor antagonists (GLP-1 RAs) are gastrointestinal (GI) events, most notably vomiting, nausea and diarrhea. Pooled data from trials comparing lixisenatide to placebo demonstrated a 22% increased incidence of adverse GI events in patients treated with lixisenatide, leading to discontinuation in 4.3% of patients taking lixisenatide versus 0.5% of patients treated with placebo.[12]
- The glucose-dependent mechanism of action of lixisenatide lends itself to a low incidence of hypoglycemia. Lixisenatide had a 2-25% higher incidence of hypoglycemia compared to placebo; however, risk was highly dependent upon background therapy with the greatest risk in patients also taking a SU or insulin.[12] Symptomatic hypoglycemia was defined as symptoms of hypoglycemia and a glucose level less than 60 mg/dL or prompt recovery after glucose or carbohydrate administration.[1-11]
- Withdrawal rates due to adverse events are an important assessment of tolerability. In all studies lixisenatide had higher early withdrawal rates due to adverse events. In placebo-controlled comparisons, lixisenatide was associated with approximately 10% of early withdrawals due to adverse events compared to 7% with placebo.[1-7] In active treatment comparisons, the average early withdrawal rate for lixisenatide was 6% versus 4% with comparators.[8-10]

Recommendations:

- Make lixisentide non-preferred as it offers no evidence for advantage in terms of comparative efficacy or safety. Approval is subject to current PA criteria for GLP-1 receptor agonists (See Appendix 3).

Background:

GLP-1 RAs are a class of antidiabetic treatments approved for subcutaneous use in patients with T2DM to lower HbA1c. GLP-1 RAs work by glucose-dependent insulin secretion and prevention of glucagon release. The mechanism of action of GLP-1 analogs result in reduced postprandial glucose (PPG) levels and reduced GI motility.[12] There are 5 GLP-1 RAs approved by the FDA: albiglutide, exenatide (including an extended-release formulation), dulaglutide, liraglutide and lixisenatide.[13] The extended-release formulation of exenatide, albiglutide, and dulaglutide are administered once weekly; exenatide is administered twice daily; and all other GLP-1 RAs are administered once a day. In addition to glucose-lowering effects, GLP-1 RAs are associated with modest weight loss, low risk of hypoglycemia, and small changes in blood pressure. GLP-1 RAs have also shown to decrease PPG levels; however, clinical significance of targeting PPG specifically has yet to be shown to result in improved health outcomes.[13] The adverse events most associated with GLP-1 RAs are GI-related (nausea, vomiting and diarrhea) which most commonly occur within the first 3-4 weeks of therapy. Dose titration of the GLP-1 RAs is recommended over a 2-4 weeks to minimize this effect.[14] Rare but serious adverse events associated with GLP-1 RAs are increased risk of pancreatitis, bile duct and gallbladder disease, and medullary thyroid carcinoma which has been observed in rodent models.[14]

Clinical practice guidelines recommend a goal A1c of less than 7% for most patients with T2DM, but goals of less than 6.5% or less than 8% may be reasonable depending on patient-specific factors, such as concomitant comorbidities and age.[15,16] Important clinical outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, and serious adverse events (SAE) including symptomatic hypoglycemia. Hemoglobin A1c is used as a surrogate marker to assess comparative efficacy of different diabetes agents in clinical trials, but management of hyperglycemia is associated with improved microvascular complications and possibly macrovascular outcomes as well.[15,16] Available data for most newer diabetes drugs are limited to short-term studies, which prevents the assessment of the durability of glucose lowering effects long-term and prevents comparison of impact on microvascular and macrovascular complications.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) guidelines recommend either a GLP-1 RA, sodium-glucose transporter-2 (SGLT-2) inhibitor, dipeptidyl peptidase-4 (DPP-4) inhibitor, α-glucosidase inhibitor, sulfonylurea (SU) or thiazolidinedione (TZD) as an option for patients who have hyperglycemia despite maximally tolerated metformin therapy.[15,16] An updated position statement by the American Diabetes Association (ADA) also suggests a role for GLP-1 RAs in patients on basal insulin that require additional glucose lowering.[15] However, the National Institute for Health and Care Excellence (NICE) recommends GLP-1 RAs as a third-line option in addition to metformin and a SU.[17] The Oregon Health & Science University Drug Effectiveness Review Project (DERP) found glucose lowering and incidence of GI events were similar between the GLP-1 RAs.[13]

Lixisenatide in the most recently approved GLP-1 RA in the United States, which follows the European approval in 2013.[5] The focus of this review is to evaluate the evidence related to the approval of lixisenatide and to provide recommendations for the Oregon Health Plan (OHP) fee-for-service Preferred Drug List (PDL) and recommendations for clinical prior authorization (PA) criteria, if appropriate.

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Lixisenatide is given as a 20 mcg subcutaneous injection one hour before the first meal of the day.[12] Lixisenatide should be initiated at 10 mcg for 2 weeks and then titrated to 20 mcg if tolerated. Efficacy and safety data for lixisenatide are available from 14 clinical trials. Eleven trials have been published and are discussed below. Three trials were not applicable to the OHP population due to being studied exclusively in Asian countries and were therefore not included. The primary endpoint in all but two trials was change in A1c from baseline with secondary endpoints that included changes in body weight and number of patients who obtained an A1c less than 7%.[1-8,10] One trial assessed a composite primary endpoint of 2 unrelated outcomes: the percent of patients obtained an A1c less than 7% and weight loss more than 5%.[9] Another trial was a cardiovascular (CV) study which analyzed the composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization for unstable angina.[11]

Placebo-controlled Trials

Fonseca, et al.
In a 12-week, double-blind, placebo-controlled trial, 361 patients were randomized to once daily subcutaneous lixisenatide 2-step (10 mcg for one week, 15 mcg for one week, then 20 mcg), lixisenatide 1-step (10 mcg for 2 weeks then 20 mcg) or placebo 2-step or placebo 1-step (results combined).[1] Included patients were treatment-naïve with T2DM, baseline A1c of 8.04%, mean age of 54 years and 52% were males. Lixisenatide 2-step reduced A1c by 0.73%, lixisenatide 1-

step by 0.85% and placebo by 0.19%. Both lixisenatide treatments were statistically superior to placebo in terms of A1c reduction compared to placebo, with a difference of -0.54% for lixisenatide 2-step and -0.66% for lixisenatide 1-step (p<0.0001 for both, no CI provided).[1] The number of patients who obtained an A1c less than 7% was 52% with lixisenatide 2-step, 47% with lixisenatide 1-step and 27% for placebo (p<0.01 for both vs. placebo). All groups experienced weight loss with a mean change of 2 kg. Study limitations include the short study duration, the use in patients that were treatment-naïve (metformin is recommended first line by guidelines), the lack of complete statistical analyses (i.e., confidence intervals) and lack of detail on blinding methods which can all introduce biases into the study.

Riddle, et al.

Lixisenatide was studied in a 24-week, randomized, double-blind, phase 3 study in patients with T2DM taking metformin with or without a SU, TZD and/or meglitinide analog (e.g., repaglinide).[2] Patients had a 9.2-year history of diabetes, mean A1c of 7.6%, were 56 years of age and predominately white (74%). After discontinuation of other antidiabetic agents other than metformin, a 12-week run-in period was used to add insulin glargine to patients' regimens. Insulin glargine doses were titrated weekly to a fasting range of 80-100 mg/dL. If after initial titration of insulin glargine during the run-in period the A1c remained greater than or equal to 7% but less than or equal to 9%, those patients were randomized to lixisenatide 20 mcg or placebo. Both groups were on background metformin and insulin glargine.[2] Patients in the lixisenatide group experienced a change in A1c of -0.7% compared to -0.4% in the placebo group (least square mean difference [LSMD] -0.3%; 95% CI, -0.5 to -0.2%; p<0.0001). The number of patients who obtained an A1c less than 7% was higher in the lixisenatide group compared to placebo (56% vs. 39%, respectively). There was a 0.3 kg weight gain in the lixisenatide group compared to a 1.2 kg weight gain in the placebo group. Applicability of this study is limited to patients already close to A1c goal. Other study limitations included the trial duration of only 24 weeks, lack of details on blinding of patients and practitioners and high attrition rates in the lixisenatide group compared to placebo (25% vs. 10%, respectively), which could bias results.[2]

Ahren, et al.

Patients with elevated glucose levels despite optimal metformin therapy were randomized to subcutaneous lixisenatide 20 mcg in the morning, lixisenatide 20 mcg in the evening, placebo injection in the morning or placebo injection in the evening.[3] The study was a multicenter, double-blind trial of 680 patients with a history of T2DM for approximately 6 years. Included patients had moderately uncontrolled glucose levels indicated by a mean A1c of 8% while taking at least 1.5 g of metformin daily. Patients were a mean age of 55 years and obese (BMI 33 kg/m2). The primary endpoint was change in A1c at week 24 for lixisenatide given in the morning compared to placebo. Secondary endpoints were change in A1c in lixisenatide given in the evening compared to placebo, number of patients who obtained an A1c less than 7% and changes in weight. The study was not powered to directly compare the efficacy of lixisenatide given in the morning compared to the evening. Morning lixisenatide decreased A1c by 0.8%, evening lixisenatide decreased A1c by 0.9% and placebo decreased A1c by 0.4%.[3] The mean difference between morning lixisenatide and placebo was 0.5% (95% CI, -0.66 to -0.31%; p<0.0001) and the difference between evening lixisenatide and placebo was 0.4% (95% CI, -0.54 to -0.19%; p<0.0001).[3] The number of patients who obtained an A1c less than 7% was not statistically different between patients who received lixisenatide or placebo regardless of time of day of administration. Many details of the study design were lacking which introduces an unclear risk of bias and reduced confidence in the results.

Bolli, et al.

In a 24 week, double-blind, placebo-controlled trial lixisentide was compared to placebo in patients with T2DM and treated with metformin.[4] Patients were randomized to one of 4 groups: subcutaneous lixisenatide 2-step (10 mcg for one week, 15 mcg for one week, then 20 mcg), lixisenatide 1-step (10 mcg for 2 weeks then 20 mcg) or placebo 2-step or placebo 1-step (results combined). Included patients had a 6-year history of T2DM, mean A1c of 8%, were predominately white and were taking metformin 1.5 g/day for at least 3 months. Results were analyzed with a mITT analysis with LOCF used for handling missing data. At week 24, decreases in A1c were as follows: -0.8% for lixisenatide 2-step, -0.9% for lixisenatide 1-step and -0.4% for placebo (CI not provided; p<0.0001

for both placebo comparisons). More patients in the lixisenatide 1-step group obtained an A1c less than 7% compared to lixisenatide 2-step and placebo (47.4%, 42.1% and 24.2%, respectively).[4] Four patients would need to be treated with lixisenatide 1-step for 24 weeks to obtain this goal compared to 6 for lixisenatide 2-step. Changes in body weight were -2.6 kg for lixisenatide 2-step, -2.7 kg for lixisenatide 1-step and -1.6 kg gain for placebo (CI not provided; p<0.01 for both vs. placebo).[4] Randomization and blinding of outcome assessors was not described and could potentially bias results. Adding lixisenatide to metformin helped to get approximately 25% more patients to an A1c goal of less than 7%; however, over 50% of patients were still not able to obtain goal A1c with lixisenetide.

Rosenstock, et al.
Patients with T2DM not controlled on a SU with our without metformin were randomized to lixisenatide 20 mcg or placebo for 24 weeks.[5] In this randomized, double-blind, phase 3 trial the mean age was 57 years, patients had a history diabetes for 9.4 years and a mean A1c of 8.3%. Patients with major comorbidities were excluded. Results were based on the mITT population (n = 822) with LOCF to account for missing data.[5] Lixisenatide lowered A1c by -0.85% and placebo lwered A1c by -0.10% (LSMD -0.74%; 95% CI, -0.867 to -0.621%; p<0.0001). More patients were able to obtain an A1c less than 7% with lixisenatide (36.4% vs. 13.5%, respectively). Lixisenatide use was shown to decrease weight more than placebo (LSMD -0.85 kg; 95% CI, -1.25 to -0.42; p<0.0001).[5] Many details on blinding and randomization were not described leading to a risk of selection, performance and detection bias.

Pinget, et al.
Lixisenatide was studied in patients with moderately uncontrolled T2DM despite treatment with pioglitazone with or without metformin. In this phase 3, double-blind, multicenter trial, 484 patients were randomized to lixisenatide 20 mcg or placebo for 24 weeks with a variable extension option of at least 52 weeks.[6] Patients were a mean age of 56 years with moderately elevated glucose levels (A1c 8.1%). A majority of patients were obese (67.6%). The target dose of lixisenatide was 20 mcg after a 2-week dose titration phase. Results were analyzed in the mITT population using LOCF for missing data. Patients were on a median pioglitazone dose of 30 mg; 81% of patients were also taking metformin at a median daily dose of 2000 mg. Hemoglobin A1c was reduced by 0.9% with lixisenatide and reduced by 0.34% with placebo (LSMD 0.56%; 95% CI, -0.73 to -0.39%; p<0.0001).[6] There were more patients in the lixisenatide group that achieved an A1c of less than 7% (52.3% vs. 26.4%; NNT =4). Subgroup analysis on metformin use, race, gender, BMI and baseline A1c did not influence results. Changes in body weight were not statistically significant between groups (LSMD -0.41 kg; 95% CI, -1.03 to 0.20 kg; p=0.1864).[6] Details on blinding of providers and patients may introduce detection bias. Applicability of these results to non-white populations is limited.

Riddle, et al.
Patients with a history of T2DM over 12 years were randomized to lixisenatide and placebo after failure to obtain glucose control with basal insulin with or without metformin.[7] The study was a 24-week, double-blind, phase 3 trial in 495 patients across multiple countries. Patients had at least a 3-month history of using insulin and metformin (if applicable), were mean age of 57 years, and had a baseline A1c of 8.4%. Use of basal insulin was predominately with insulin glargine (50%) or NPH (40%). Results were analyzed using mITT with LOCF for missing data. Lixisenatide lowered A1c by -0.7% compared to -0.4% in the placebo group (LSMD 0.4% (95% CI -0.6 to -0.2%; p=0.0002). Twenty-eight percent of the patients in the lixisenatide group obtained an A1c less than 7% compared to 12% in the placebo group (p<0.0001). Changes in weight were -1.8 kg for lixisenatide and -0.5 kg for placebo.[7] Extrapolation of results would be most appropriate in white patients who already on a basal insulin and metformin who are already close to achieving their A1c goal. Other limitations include short study duration and predominantly white population.

Active Treatment Comparisons

Rosenstock, et al.
In a noninferiority trial, lixisenatide was compared to exenatide in patients taking metformin over 24 weeks.[8] The trial was open-label, parallel-group, phase 3 study in patients with a history of T2DM for approximately 7 years. Most patients were white (93%) with a mean age of 57 years and a baseline A1c of 8%. Lixisenatide was titrated over 2 weeks to a target dose of 20 mcg daily and exenatide was titrated over 4 weeks to a target dose of 10 mcg twice daily. Data were analyzed in the mITT population with a noninferiority margin set at 0.4% for the upper limit of the 95% CI. Lixisenatide was found to be noninferior to exenatide at lowering A1c. Hemoglobin A1c reductions were -0.79% with lixisenatide and -0.96% for exenatide (LSMD 0.17%; 95% CI, -0.033 to 0.297%).[8] There were a similar number of patients who obtained an A1c less than 7% in each group (48.5% and 49.8%, respectively). Changes in weight were -2.96 kg for patients on lixisenatide and -3.98 kg for exenatide-treated patients.[8] The high percentage of white patients limits the applicability of the results to other races and ethnicities. The short trial duration limits the ability to determine long term differences between treatments. The open-label study design increases risk for detection and performance bias.

Van Gaal, et al.
In a double-blind, 24-week, randomized trial, subcutaneous lixisenatide 20 mcg was compared to oral sitagliptin 100 mg in obese patients (n=319) less than 50 years of age with T2DM.[9] Patients had a mean baseline A1c of 8.1%, were mostly white (81%) with a mean age of 43 years and BMI of 36.8 mg/k^2. Patients had similar baseline characteristics except the lixisenatide group had 10% fewer males than the sitagliptin group. The data were analyzed using mITT design with LOCF for missing data. The primary composite endpoint was the number of patients who obtained an A1c less than 7% and weight loss of at least 5%, an interesting composite of 2 unrelated endpoints. Secondary endpoints were similar to the other studies. There was no statistically significant difference an achievement of goal A1c plus 5% weight loss between lixisenatide and sitagliptin (12% vs. 7.5%, respectively; LSMD 4.6%; 95% CI, -1.8 to 11.0%; p=0.1696).[9] The number of patients who obtained an A1c less than 7% was the same in both groups (40%); glucose lowering (-0.7%) was also about the same. Weight loss of 2.5 kg was observed in the lixisenatide group compared to weight loss of 1.2 kg in sitagliptin patients (p=0.0006). A 10% difference in gender between the groups could impact the results of such a small study. Additionally, lack of details on randomization and blinding allows for an unclear risk of bias. The results of this study are most likely to apply to younger obese T2DM patients.

Rosenstock, et al.
In an open-label, noninferiority, phase 3 trial, lixisenatide was studied in uncontrolled T2DM patients taking once daily rapid-acting insulin glulisine or three times daily insulin glulisine in addition to insulin glargine with or without metformin.[10] Patients meeting inclusion criteria had a 12+ year history of T2DM, mean A1c of 8.4% and a mean age of 60 years. Ninety percent were taking metformin in addition to a mean dose of 55 units/day of insulin glargine as background therapy. All other oral antidiabetic (OAD) therapies besides metformin were discontinued. After randomization, glargine doses were titrated weekly to achieve a fasting glucose of 80-100 mg/dL for the first 4 weeks. There were 3 co-primary endpoints: noninferiority of lixisenatide compared to glulisine once daily in A1c reduction; lixisenatide compared to glulisine three times daily for noninferiority in A1c reduction; or superiority of lixisenatide compared to glulisine three times daily in change in body weight. Lixisenatide and daily insulin glulisine lowered A1c by -0.6% and glulisine three times daily lowered A1c by -0.8%, which met the noninferiority margin for both. The highest number of patients who obtained an A1c less than 7% was in the three times daily glulisine group (49%), followed by lixisenatide-treated patients (42%) and the once daily glulisine group (38%). Patients in the lixisenatide group lost 0.6 kg of body weight compared to weight gains in the once daily and three times daily glulisine groups (1.0 kg and 1.4 kg, respectively); however, differences were not statistically significant.[10] The open-label study design introduces performance bias and the short trial duration limits the ability to assess clinically meaningful long-term efficacy and safety outcomes.

Cardiovascular Study

Pferrer, et al.
Lixisenatide was studied in a double-blind, multicenter, placebo-controlled, randomized trial in patients with a history of T2DM and acute coronary syndrome (ACS) diagnosis within 180 days of screening.[11] Patients were randomized to lixisenatide (n=3031) or placebo (n=3032) injected subcutaneously for a median of 25 months. Twenty-six percent of patients were seen in the US. Patients were on average 60 years of age with a 9-year or more history of T2DM, A1c of 7.7%, 69% male and 75% white. A majority (90%) of patients were on an additional diabetes medication, the most common being metformin (63%) and sulfonylureas (31%). A similar number of patients in each group were on background therapy at baseline. Eighty-five percent of patients were taking an angiotensin receptor blocker (ARB) or ACE inhibitor and 84% were also on a beta-blocker. Qualifying ACS events were non ST-elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), or unstable angina (0.2% were unclassified in each group). The trial was event-driven with the primary analysis conducted in the ITT population. Noninferiority was determined if the upper boundary of the 95% confidence interval (CI) of the hazard ratio (HR) was less than 1.3 and superiority would be found if the upper boundary was less than 1.0. The primary endpoint was the composite of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization from unstable angina. Key secondary endpoints were hospitalization for heart failure (HF) and death from any cause. Lixisenatide was found to be noninferior to placebo for the primary endpoint but not superior. Occurrence of the primary endpoint was 13.4% in the lixisenatide group and 13.2% in the placebo group (HR 1.02; 95% CI, 0.89 to 1.17).[11] The most common event type in both groups were nonfatal MI events (61.9% in the placebo group and 62.8% in the lixisenatide group). Rates of hospitalizations due to HF were similar between groups with an incidence of 4% in patients on lixisenatide and 4.2% of patients taking placebo (HR 0.96; 95% CI, 0.75 to 1.23; p=0.75). There was a 7.2% incidence of death in the placebo group compared to 7.0% in the lixisenatide group (p=0.50).[11] This study shows that in patients who meet the inclusion criteria, lixisenatide does not decrease risk of a cardiovascular events.

Clinical Safety:
Common adverse reactions associated with lixisenatide are presented in Table 1. Lixisenatide was associated with a higher incidence of adverse GI events, mostly mild to moderate, compared to placebo in pooled placebo-controlled trials, with 39.7% of patients in the lixisenatide group with an event compared to 18.4% in the placebo group.[12] Early discontinuation rates due to adverse GI events were 4.3% of patients int the lixisenatide groups compared to 0.5% in the placebo groups. Hypoglycemia associated with clinical symptoms, a glucose level less than 60 mg/dL or a quick recovery of symptoms after administration of a glucose or other carbohydrate was more common in lixisenatide treated-patients and occurred up to 25% more often than placebo-treated patients. Hypoglycemia risk was dependent on background therapies with the highest risk seen in patients also taking insulin or a SU, or when lixisenatide was given at night compared to the morning. Severe hypoglycemia, defined as clinical symptoms that require assistance from another person or a glucose level less than 36 mg/dL, rarely occurred.[1-12] Lixisenatide can be used in patients with moderate renal impairment (estimated creatinine clearance (CrCl) of 30 to less than 60 mL/min/1.73 m^2) but use in severe renal failure is not advised. Rare but serious adverse reactions include acute kidney injury or worsening of chronic renal failure, pancreatitis and risk for anaphylaxis. Antibody development to lixisenatide has been seen in 70% of patients involved in clinical trials with 2.4% having an attenuated response to treatment.[12]

Table 1. Adverse Reactions occurring in ≥5% of patients treated with lixisenatide[12]

Adverse Reaction	Placebo (n=1639)	Lixisenatide (n=2869)
Nausea	6%	25%
Vomiting	2%	10%
Headache	6%	9%
Diarrhea	6%	8%
Dizziness	4%	7%

Pharmacology and Pharmacokinetic Properties: Lixisenatide[12]

Parameter	
Mechanism of Action	GLP-1 RA which increases glucose-dependent insulin release, decreases glucagon secretion and slows gastric emptying
Absorption	1-3.5 hours when given subcutaneously
Distribution and Protein Binding	100 L
Metabolism	Glomerular filtration and proteolytic degradation
Half-Life	3 hours
Elimination	Glomerular filtration and proteolytic degradation

Abbreviations: RA – receptor antagonist

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Number of patients obtaining an A1c<7%
2) Mortality
3) Macrovascular outcomes
4) Microvascular outcomes

Primary Study Endpoint:

1) Change in A1c from baseline
2) Composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization from unstable angina
3) Composite endpoint of number of patients with an A1c less than 7% and weight loss of at least 5%

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/N NH	Risk of Bias/ Applicability
Placebo-controlled Trials								
1. Fonseca, et al.[1] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 2-step (L2)* 2. Lixisenatide 1-step (L1)^ 3. Placeboł Duration: 12 weeks * 10 mcg SC daily for 1 week, 15 mcg SC daily for 1 week, and then 20 mcg SC daily ^ 10 mcg SC daily for 2 weeks, then 20 mcg SC daily ł placebo 2-step and placebo 1-step results were combined (same dosing pattern as for lixisenatide 2-step and lixisenatide 1-step)	Demographics: Mean age: 54 yrs Males: 52% White: 72% Baseline A1c: 8.04% Duration of DM: 1.3 yrs. Key Inclusion Criteria: - Age 20-85 years - T2DM - Treatment naïve - A1c ≥7.0% to ≤10% Key Exclusion Criteria: - Prior use of an antidiabetic agent - FPG >250 mg/dL - Elevated pancreatic enzymes - GI disease - Pancreatitis - History of N/V - GI surgery - CVD - Hepatic disease - Renal disease	mITT: L2:120 L1: 119 P: 122 PP: L2: 110 L1: 108 P: 113 Attrition: L2: 8.3% L1: 9.2% P: 7.4%	Primary Endpoint: Change from baseline A1c: L2: -0.73% L1: -0.85% P: -0.19% L2 vs P: LSMD -0.54% (CI not reported) p<0.0001 L1 vs P: LSMD -0.66% (CI not reported) p<0.0001 Secondary Endpoints: Patients with A1c <7%: L2: 52% L1: 47% P: 27% P <0.01 for both comparisons to placebo Change in body weight: L2: -2 kg L1: -2 kg P: -2 kg	 NA NA 25%/4 20%/5 NS	Outcome: Serious AE: L2: 1 (0.83%) L1: 0 (0%) P: 5 (4.1%) (p-value not reported) D/C due to AE: L2: 5 (4.2%) L1: 3 (2.5%) P: 1 (0.8%) (p-value not reported) Gastrointestinal AE: L2: 39 (32.5%) L1: 38 (31.9%) P: 17 (13.9%) (p-value not reported) Symptomatic Hypoglycemia*: L2: 3 (2.5%) L1: 1 (0.8%) P: 2 (1.6%) (p-value not reported)	 NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized using an interactive voice response system. Performance Bias: (unclear) double-blind design but details not provided. Volume and dose titration was open-label. Detection Bias: (low) independent data monitoring committee. Attrition Bias: (low) attrition was low in all groups. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: patients were treatment-naïve which is rare in T2DM in which metformin is universally recommended as first line. Intervention: appropriate use of lixisenatide. Comparator: placebo comparison appropriate in this population who were recently diagnosed and receiving diet and exercise counseling. Outcomes: more A1c lowering was seen in the L1 group but less patients achieved an A1c <7% most likely to a higher baseline A1c of 8.06% compared to 7.97% in the L2 group and 8.07% in the placebo group. Change in A1c from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: sixty-nine centers and 12 countries. Number of US sites not specified.

2. Bolli, et al.[2] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 2-step + metformin (L2)* 2. Lixisentatide 1-step + metformin (L1)^ 3. Placebo + metforminł Duration: 12 weeks * 10 mcg SC daily for 1 week, 15 mcg SC daily for 1 week, and then 20 mcg SC daily ^ 10 mcg SC daily for 2 weeks, then 20 mcg SC daily ł placebo 2-step and placebo 1-step results were combined (same dosing pattern as for lixisentide 2-step and lixisenatide 1-step) Median duration: 24 weeks	Demographics: Mean age: 56 yrs Males: 45% White: 91% Baseline A1c: 8% Duration of T2DM: 6 yrs. Key Inclusion Criteria: - Age 24-79 years - T2DM ≥1 yr. - Metformin monotherapy 1.5 g/day for ≥3 mo. - A1c 7.0-10% Key Exclusion Criteria: - FPG >250 mg/dL - pancreatitis - GI surgery - IBS	Mitt: L2: 161 L1: 161 P2: 80 P1: 82 PP: L2: 144 L1: 147 P2: 78 P1: 73 Attrition: L2: 11% L1: 10% P2: 1% P1: 10%	Primary Endpoint: Change from baseline A1c: L2: -0.8% L1: -0.9% P: -0.4% L2 vs. P: LSMD -0.4 (95% CI, -0.6 to -0.2; p<0.0001) L1 vs. P: LSMD -0.5 (95% CI, -0.7 to -0.3; p<0.0001) Secondary Endpoints: Patients with A1c <7%: L2: 68 (42.1%) L1: 76 (47.4%) P: 39 (24.2%) L2 vs P: p=0.0005 L1 vs P: p<0.0001 Change in body weight: L2: -2.7 kg L1: -2.6 kg P: -1.6 kg L2 vs P: LSMD -1.1 kg (CI not provided) p<0.01 L1 vs P: LSMD -1.0 kg (CI not provided) p<0.01	NA NA 18%/6 23%/4 NA NA	Outcome: Serious AE: L2: 7 (4.3%) L1: 5 (3.1%) P: 4 (2.5%) (p-value not provided) D/C due to AE: L2: 13 (8.1%) L1: 9 (5.6%) P: 4 (2.5%) (p-value not reported) Gastrointestinal AE: L2: 76 (47.2%) L1: 67 (41.6%) P: 35 (2.1.9%) (p-value not reported) Symptomatic Hypoglycemia*: L2: 4 (2.5%) L1: 3 (1.9%) P: 1 (0.6%) (p-value not reported) Injection Site Reactions: L2: 7 (4.3%) L1: 7 (4.3%) P: 2 (1.3%) (p-value not reported)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) not described. Performance Bias: (low) double-blind design with matching placebo. Volume and dose titration was open-label. Detection Bias: (unclear) not described. Attrition Bias: (low) there was a 10% difference in attrition between groups. mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: patients randomized to the lixisenatide 1-step had better A1c lowering with less GI adverse events. Metformin dose was approximately 2 g/day in all groups at baseline. Intervention: appropriate use of lixisenatide. Comparator: placebo comparison (on background therapy) appropriate in this population. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: seventy-five centers and 15 countries. Number of US sites not specified.

3. Ahren, et al.[3] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC AM + metformin* (LAM) 2. Lixisenatide 20 mcg SC PM + metformin* (LPM) 3. Placebo SC AM + metformin (P)* 4. Placebo SC PM + metformin (P)* Median duration: 24 weeks * Placebo group results were combined	<u>Demographics</u>: Mean age: 55 yrs Males: 44% White: 89% Baseline A1c: 8.1% Duration of T2DM: 6.1 yrs. <u>Key Inclusion Criteria</u>: - T2DM - Metformin monotherapy ≥1.5 g/day for ≥3 mo. - A1c 7.0%-10% <u>Key Exclusion Criteria</u>: - FPG >250 mg/dL - GI surgery/GI disease - pancreatitis - antidiabetic treatments other than metformin within last 3 mo. - ketoacidosis	<u>mITT</u>: LAM: 255 LPM: 255 P: 170 <u>PP</u>: LAM: 233 LPM: 224 P: 158 <u>Attrition</u>: LAM: 8.6 % LPM: 12.2% P: 7.1%	<u>Primary Endpoint:</u> Change from baseline A1c in AM: LAM: -0.9% P: -0.4% LSMD -0.5% (95% CI, -0.66 to -0.31; p<0.0001 <u>Secondary Endpoints:</u> Change from baseline A1c in PM: LPM: -0.8% P: -0.4% LSMD -0.4% (95% CI, -0.54 to -0.19) p<0.0001 Patients with A1c <7%: LAM: (43%) LPM: (40.6%) P: 19 (22%) p<0.0001 for both Change in body weight: LAM: -2.0 kg LPM: -2.0 kg P: -1.6 kg p=NS	NA NA 21%/5 19%/5 NS	<u>Outcome</u>: <u>Serious AE</u>: LAM: 5 (2.0%) LPM: 8 (3.1%) P: 2 (1.2%) (p-value not provided) <u>D/C due to AE</u>: LAM: 18 (7.1%) LPM: 14 (5.5%) P: 2 (1.2%) (p-value not reported) <u>Gastrointestinal AE</u>: LAM: 93 (36.5%) LPM: 105 (41.2%) P: 44 (25.9%) (p-value not reported) <u>Symptomatic Hypoglycemia*:</u> LAM: 6 (2.4%) LPM: 13 (5.1%) P: 1 (0.6%) (p-value not reported) <u>Injection Site Reactions:</u> LAM: 17 (6.7%) LPM: 17 (6.7%) P: 6 (3.5%) (p-value not reported)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (high) randomization details not provided. <u>Performance Bias</u>: (unclear) double-blind design but details not provided. <u>Detection Bias</u>: (unclear) no details were provided. <u>Attrition Bias</u>: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data. <u>Reporting Bias</u>: (low) pre-specified outcomes were appropriately reported. **Applicability**: <u>Patient</u>: more patients in the placebo group were male, 48% compared to 42% in the lixisenatide group. <u>Intervention</u>: appropriate use of lixisenatide. <u>Comparator</u>: placebo comparison (on background therapy) appropriate in this population. <u>Outcomes</u>: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. <u>Setting</u>: one hundred thirty-three centers and 16 countries. US sites not specified.

4. Riddle, et al. [4] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + insulin glargine and metformin (L) 2. Placebo SC daily + insulin glargine and metformin (P) Median duration: 24 weeks	<u>Demographics</u>: Mean age: 56 yrs Males: 50% White: 74% Baseline A1c: 7.6% Duration of DM: 9.2 yrs. <u>Key Inclusion Criteria</u>: - BMI >20 kg/m2 - T2DM ≥1 yr. - Metformin use for 3 months ± SU, Meglitinide and/or TZD - A1c ≥7.0% to ≤10% <u>Key Exclusion Criteria</u>: - Prior use of an antidiabetic agent other than SU, TZD or meglitinide last 3 months - Use of weight loss drugs if not at stable dose for ≥3 mo. - Hypoglycemia awareness - GI disease	<u>Mitt</u>: L:223 P: 223 <u>PP</u>: L: 194 P: 211 <u>Attrition</u>: L: 25% P: 10%	<u>Primary Endpoint:</u> Change from baseline A1c: L: -0.7% P: -0.4% LSMD -0.3 (95% CI, -0.5 to -0.2; p<0.0001 <u>Secondary Endpoints:</u> Patients with A1c <7%: L: 121 (56%) P: 85 (39%) p=0.0001 Change in body weight: L: 0.3 kg P: 1.2 kg LSMD -0.9 kg (95% CI, -1.4 to -0.4; p=0.0012	 NA 17%/6 NA	<u>Outcome</u>: <u>Serious AE</u>: L: 17 (7.6%) P: 10 (4.5%) (p-value not reported) <u>D/C due to AE</u>: L: 19 (8.5%) P: 8 (3.6%) (p-value not reported) <u>Gastrointestinal AE</u>: L: 89 (39.9%) P: 36 (16.1%) (p-value not reported) <u>Symptomatic Hypoglycemia*:</u> L: 50 (6.7%) P: 5 (2.2%) (p-value not reported) <u>Injection Site Reactions:</u> L: 15 (22.4%) P: 30 (13.3%) (p-value not reported)	 NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (low) centrally randomized 1:1 with an interactive voice response system. <u>Performance Bias</u>: (unclear) double-blind design but details not provided. Volume and dose titration was open-label. <u>Detection Bias</u>: (low) outcome assessors blinded to treatment allocation. <u>Attrition Bias</u>: (high) there was a 10% difference between groups in attrition rates. mITT with LOCF was used to analyze data. <u>Reporting Bias</u>: (low) pre-specified outcomes were appropriately reported. **Applicability**: <u>Patient</u>: population had high external validity except for low numbers of non-white participants. Higher number of discontinuations in the lixisenatide group suggests issues with tolerability. <u>Intervention</u>: appropriate use of lixisenatide. <u>Comparator</u>: placebo comparison (on background therapy) appropriate in this population. <u>Outcomes</u>: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. <u>Setting</u>: one hundred forty centers and 25 countries. Number of US sites not specified.

5. Rosenstock, et al.[5] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + SU ± metformin (L) 2. Placebo SC daily + SU ± metformin (P) Median duration: 24 weeks	Demographics: Mean age: 57 yrs Males: 51% White: 52.2% Baseline A1c: 8.3% Duration of DM: 9.4 yrs. Key Inclusion Criteria: - 20-79 years - T2DM - SU ± metformin - A1c 7.0-10% Key Exclusion Criteria: - Prior use of an antidiabetic agent other than metformin or SU in the prior 3 months - FPG >250 mg/dL - CV disease - End-stage renal disease - GI disease - HTN - Elevated LFTs - Elevated pancreatic enzymes	mITT: L: 554 P: 274 PP: L: 499 P: 255 Attrition: L: 12.9% P: 10.8%	Primary Endpoint: Change from baseline A1c: L: -0.85% P: -0.10% LSMD -0.74% (95% CI, -0.867 to -0.621; p<0.0001) Secondary Endpoints: Patients with A1c <7%: L: 201 (36.4%) P: 38 (13.5%) p<0.0001 Change in body weight: L: -1.76 kg P: -0.93 kg LSMD -0.85 kg (95% CI, -1.25 to -0.42; p<0.0001)	NA 23%/4 NA	Outcome: Serious AE: L: 20 (3.5%) P: 16 (5.6%) (p-value not reported) D/C due to AE: L: 56 (9.8%) P: 14 (4.9%) (p-value not reported) Gastrointestinal AE: L: 235 (40.9%) P: 57 (20.0%) (p-value not reported) Symptomatic Hypoglycemia*: L: 88 (15.3%) P: 35 (12.3%) (p-value not reported) Injection Site Reactions: L: 26 (4.5%) P: 5 (1.8%) (p-value not reported)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (high) randomized in a 2:1. Details not provided. Performance Bias: (unclear) double-blind design but details not provided. Detection Bias: (unclear) no details were provided. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: 84% were also taking metformin at time of randomization. Intervention: appropriate use of lixisenatide. Comparator: placebo comparison (on background therapy) appropriate in this population. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred thirty-six centers and 16 countries. Number of US sites not specified.

6. Pinget, et al.[6] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + pioglitazone ± metformin (L) 2. Placebo SC daily + pioglitazone ± metformin (P) Median duration: 24 weeks	Demographics: Mean age: 57 yrs Males: 53% White: 84% Baseline A1c: 8.1% Duration of T2DM: 8.1 yrs. Key Inclusion Criteria: - Age ≥18 years - T2DM - Pioglitazone ≥30 mg/day ± metformin in previous 3 months - A1c ≥7.0% to ≤10% Key Exclusion Criteria: - Prior use of an antidiabetic agent other than pioglitazone or metformin in the prior 3 months - FPG >250 mg/dL - CV disease - End-stage renal disease - GI disease - pancreatitis - Elevated LFTs	mITT: L: 308 P: 148 PP: L: 288 P: 137 Attrition: L: 10.8% P: 14.9%	Primary Endpoint: Change from baseline A1c: L: -0.9% P: -0.34% LSMD -0.56% (95% CI, -0.73 to -0.39; p<0.0001 Secondary Endpoints: Patients with A1c <7%: L: 161 (52.3%) P: 39 (26.4%) p<0.0001 Change in body weight: L: -0.2 kg P: 0.2 kg LSMD -0.41 kg (95% CI, -1.03 to -0.20; p=0.1864	NA 26%/4 NS	Outcome: Serious AE: L: 8 (2.5%) P: 3 (1.9%) (p-value not reported) D/C due to AE: L: 21 (6.5%) P: 8 (5.0%) (p-value not reported) Gastrointestinal AE: L: 118 (36.5%) P: 46 (28.6%) (p-value not reported) Symptomatic Hypoglycemia*: L: 11 (3.4%) P: 2 (1.2%) (p-value not reported) Injection Site Reactions: L: 13 (4.0%) P: 7 (4.3%) (p-value not reported)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 2:1 by an interactive voice response system. Performance Bias: (unclear) double-blind design but details not provided. Detection Bias: (low) independent data monitoring committee. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: 81% were also taking metformin at time of randomization and 92% of patients were able to tolerate the 20 mcg dose of lixisenatide. Intervention: appropriate use of lixisenatide. Comparator: placebo comparison (on background therapy) appropriate in this population. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred fifty centers and 13 countries. Almost half of study sites were in North America.

7. Riddle, et al.[7] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + basal insulin therapy* (L) 2. Placebo SC daily + basal insulin therapy* (P) Median duration: 24 weeks * Metformin therapy was allowed if taking before enrollment	Demographics: -Mean age: 57 yrs -Males: 46% -White: 78% -Baseline A1c: 8.4% -Duration of DM: 12.5 yrs. Key Inclusion Criteria: -≥18 years -T2DM ≥1 year -Insulin ≥20 units/day for ≥3 months on stable dose -A1c 7.0%-10% -Stable metformin dose ≥1.5 g/day for ≥3 months Key Exclusion Criteria: -BMI ≤20.0 kg/m2 -Weight change >5.0 kg over 3 months -FPG >250 mg/dL -End-stage renal disease -pancreatitis -pregnancy	mITT: L: 327 P: 166 PP: L: 275 P: 147 Attrition: L: 16% P: 12%	Primary Endpoint: Change from baseline A1c: L: -0.7% P: -0.4% LSMD -0.4% (95% CI, -0.6 to -0.2; p=0.0002 Secondary Endpoints: Patients with A1c <7%: L: 86 (28%) P: 19 (12%) p<0.0001 Change in body weight: L: - 1.8 kg P: -0.5 kg LSMD -1.3 kg (95% CI, -1.8 to -0.7; p<0.0001	NA 16%/6 NA	Outcome: Serious AE: L: 12 (3.7%) P: 7 (4.2%) (p-value not reported) D/C due to AE: L: 25 (7.8%) P: 8 (4.8%) (p-value not reported) Gastrointestinal AE: L: 132 (40.2%) P: 34 (20.4%) (p-value not reported) Symptomatic Hypoglycemia*: L: 87 (26.5%) P: 35 (21.0%) (p-value not reported) Injection Site Reactions: L: 4 (1.2%) P: 1 (0.6%) (p-value not reported)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) centrally randomized 2:1 and allocated via an interactive voice response system. Performance Bias: (low) double-blind design but details not provided. Detection Bias: (low) investigators and data analysts unaware of study assignments. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: patients has a mean basal insulin dose of 55 units/day and over 3 year history of insulin use at time of enrollment. Metformin use was 79% at baseline. Intervention: appropriate use of lixisenatide. Comparator: placebo comparison (on background therapy) appropriate in this population. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred and eleven centers and 15 countries.

Active Treatment Comparison Trials								
8. Rosenstock, et al.[8] MC, PG, OL, PC, Phase 3, noninferiority Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + metformin (L) 2. Exenatide 10 mcg SC twice daily + metformin (E) Median duration: 24 weeks	Demographics: Mean age: 57 yrs Males: 53% White: 93% Baseline A1c: 8.02% Duration of T2DM: 6.8 yrs. Key Inclusion Criteria: - Age 21-84 years - T2DM - Metformin ≥1.5 g/day in previous 3 months - A1c 7.0% to 10% Key Exclusion Criteria: - Prior use of an antidiabetic agent other than metformin in the prior 3 months - FPG >250 mg/dL - CV disease - End-stage renal disease - GI disease - pancreatitis - Elevated LFTs	mITT: L: 315 E: 315 PP: L: 277 E: 271 Attrition: L: 12.9% E: 14.2%	Primary Endpoint: Change from baseline A1c: L: -0.79% E: -0.96% LSMD 0.17% (95% CI, -0.033 to 0.297) (noninferiority met) Secondary Endpoints: Patients with A1c <7%: L: 152 (48.5%) E: 157 (49.8%) (p-value not reported) Change in body weight: L: -2.96 kg E: -3.98 kg LSMD 1.02 kg (95% CI, 0.456 to 1.581) (p-value not reported)	NA NA NA	Outcome: Serious AE: L: 9 (2.8%) E: 7 (2.2%) (p-value not reported) D/C due to AE: L: 33 (10.4%) E: 41 (13%) (p-value not reported) Gastrointestinal AE: L: 137 (43.1%) E: 160 (50.6%) (p-value not reported) Symptomatic Hypoglycemia*: L: 8 (2.5%) E: 25 (7.9%) (p-value not reported)	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 1:1 by a centralized interactive voice response system. Performance Bias: (high) open-label study design. Detection Bias: (unclear) not described. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: median metformin dose was 2,039 mg at baseline. There were 11% more males in the exenatide group compared to lixisenatide. Intervention: appropriate use of lixisenatide. Comparator: exenatide dose and titration according to manufacturer's recommendation. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred twenty-two centers and 18 countries. Almost half of study sites were in North America.

9. Van Gaal, et al.[9] MC, PG, DB, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily (L) 2. Sitagliptin 100 mg PO daily (S) Median duration: 24 weeks	Demographics: Mean age: 43 yrs Males: 40% White: 81% Baseline A1c: 8.1% Duration of T2DM: 4.4 yrs. Key Inclusion Criteria: - Age ≥18 and <50 years - T2DM ≥1 year - Metformin ≥1.5 g/day in previous 3 months - A1c ≥7.0% to ≤10% - BMI ≥30 kg/m2 Key Exclusion Criteria: - FPG >250 mg/dL - CV disease - GI surgery - Pancreatitis - Abnormal pancreatic enzymes - IBS - Diabetic ketoacidosis	mITT: L: 158 S: 161 PP: L: 142 S: 150 Attrition: L: 10.1% S: 6.8%	Primary Endpoint: Composite of proportion of patients obtaining an A1c <7% and body weight loss of ≥5%: L: 12.0% S: 7.5% MD 4.6% (95% CI, -1.8 to 11.0; p=0.1696 Secondary Endpoints: Patients with A1c <7%: L: 64 (40.7%) S: 64 (40.0%) MD 0.8% (95% CI, -9.7 to 11.3; p=0.884 Change from baseline A1c: L: -0.7% S: -0.7% LSMD 0.1% (95% CI, -0.2 to 0.3; p=0.6042 Change in body weight: L: -2.5 kg S: -1.2 kg LSMD -1.3 kg (95% CI, -2.1 to -0.6; p=0.0006	 NS NS NA NA	Outcome: Serious AE: L: 3 (1.9%) S: 3 (1.9%) (p-value not reported) D/C due to AE: L: 4 (2.5%) S: 5 (3.1%) (p-value not reported) Gastrointestinal AE: L: 48 (30.4%) E: 34 (21.1%) (p-value not reported) Symptomatic Hypoglycemia*: L: 1 (0.6%) S: 3 (1.9%) (p-value not reported)	 NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) no details provided. Performance Bias: (unclear) stated that it was double-blind and double-dummy but no other details were provided. Detection Bias: (unclear) not described. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: a lower proportion of males by 10% were randomized to lixisenatide compared to sitagliptin. Patients on metformin to be included in study but metformin use during the study was not described. All patients were under 50 years and were obese (BMI 37 kg/m2). Intervention: appropriate use of lixisenatide. Comparator: sitagliptin dose appropriate. Outcomes: Difference in primary endpoints was driven by more weight loss in lixisenatide patients compared to sitagliptin. A1c lowering was the same. Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred twenty-two centers and 18 countries. Almost half of study sites were in North America.

10. Rosenstock, et al.[10] MC, PG, OL, Phase 3, noninferiority Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + insulin glargine ± metformin (L) 2. Insulin glulisine 1-1X/day + insulin glargine ± metformin (GQD) 3. Insulin glulisine 1-3X/day + insulin glargine ± metformin (GTID) Median duration: 26 weeks	<u>Demographics</u>: Mean age: 60 yrs Males: 45% Baseline A1c: 8.5% Duration of T2DM: 12.2 yrs. Insulin use: 3.2 yrs. <u>Key Inclusion Criteria</u>: - Age >18 years - T2DM ≥1 year - ≥6 mo. basal insulin use ± 1-3 OADs - A1c 7.5-10.0% if on basal insulin or metformin; A1c 7.0-10.0% if on basal insulin an SU and/or a DPP-4 inhibitor and/or meglitinide - FPG ≤140 mg/dL - BMI >20.0-40.0 kg/m2 <u>Key Exclusion Criteria</u>: - pancreatitis - calcitonin >20 pg/mL - GI disease - Elevated LFTs - Elevated pancreatic enzymes	<u>mITT</u>: L: 297 GQD: 298 GTID: 295 <u>PP</u>: L: 268 GQD: 281 GTID: 285 <u>Attrition</u>: L: 10.1% GQD: 5.7% GTID: 4.0%	<u>Primary Endpoint:</u> Change from baseline A1c: L: -0.6% GQD: -0.6% GTID: -0.8% L vs. GQD: LSMD -0.1% (95% CI, -0.17 to 0.06) (noninferiority met) L vs. GTID: LSMD -0.2% (95% CI, 0.10 to 0.33) (noninferiority met) <u>Secondary Endpoints:</u> Patients with A1c <7%: L: 123 (42.1%) GQD: 112 (38.4%) GTID: 145 (49.2%) (p-value not reported) Change in body weight: L: -0.6 kg GQD: 1.0 kg GTID: 1.4 L vs. GQD LSMD -1.7 kg (95% CI, -2.26 to -1.06) (p-value not reported) L vs. GTID LSMD -2.0 (95% CI, 2.59 to 1.40; p<0.0001)	 NA NA NA NA NA	<u>Outcome</u>: <u>Serious AE</u>: L: 11 (3.7%) GQD: 11 (3.7%) GTID: 14 (14.8) (p-value not reported) <u>D/C due to AE</u>: L: 15 (5%) GQD: 2 (0.7%) GTID: 3 (1.0%) (p-value not reported) <u>Gastrointestinal AE</u>: L: 105 (35.2%) GQD: 26 (8.6%) GTID: 22 (7.5%) (p-value not reported) <u>Symptomatic Hypoglycemia*:</u> L: 107 (35.9%) GQD: 140 (46.5%) GTID: 154 (52.4%) L vs. GQD: P =0.01 L vs. GTID: P=0.0001	 NA NA NA 11%/9 17%/6	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (low) randomized 1:1 by interactive voice or web response system. <u>Performance Bias</u>: (high) open-label study design. <u>Detection Bias</u>: (unclear) no details were provided. <u>Attrition Bias</u>: (low) attrition low with less than a 10% difference between groups. MITT with LOCF was used to analyze data. <u>Reporting Bias</u>: (low) pre-specified outcomes were appropriately reported. **Applicability**: <u>Patient</u>: 90% were also taking metformin and glargine dose was 66 units/day at time of randomization. Most patients were obese with a long history of diabetes. <u>Intervention</u>: appropriate use of lixisenatide. <u>Comparator</u>: insulin glulisine (on background therapy) appropriate in this population. <u>Outcomes</u>: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. <u>Setting</u>: one hundred ninety-nine centers and 18 countries. Number of US sites not specified.

Cardiovascular Study								
11. Pfeffer, et al.[11] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 10 - 20 mcg SC daily (L) 2. Placebo SC daily (P) Median duration: 25 months	Demographics: Mean age: 60 yrs Males: 69.3% White: 75.2% Baseline A1c: 7.7% Duration of T2DM: 9.3 yrs. Qualifying ACS: STEMI (44%), non-STEMI (38.7%) and UA (17.2%) Key Inclusion Criteria: - ACS - T2DM Key Exclusion Criteria: - Age <30 yrs - PCI within 15 days - CABG - Coronary revascularization - eGFR < 30 mL/min per 1.73 m2 - A1c < 5.5 % or > 11%	ITT: L: 3034 P: 3034 PP: L: 2922 P: 2916 Attrition: L: 29% P: 25%	Primary Endpoint: Composite of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization for UA: L: 406 (13.4%) P: 399 (13.2%) HR 1.02 (95% CI, 0.89 to 1.17; p=0.81) Secondary Endpoints: Hospitalization for HF: L: 122 (4.0%) P: 127 (4.2%) HR 0.96 (95% CI, 0.75 to 1.23; p=0.75) Death from any cause: L: 211 (7.0%) P: 223 (7.4%) HR 0.94 (95% CI, 0.78 to 1.13; p=0.50) Change in A1c: L: -0.6% P: -0.2% MD -0.27% (95% CI, -0.31 to -0.22; p<0.001)	 NS NS NS NA	Serious AE: L: 625 (20.6%) P: 699 (22.1%) (p-value not reported) D/C due to AE: L: 347 (11.4%) P: 217 (7.2%) p<0.001 Gastrointestinal AE: L: 149 (4.9%) P: 37 (1.2%) p<0.001 Hypoglycemia*: L: 504 (16.6%) P: 462 (15.2%) p=0.14	 NA 4%/25 4%/25 NS	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized using a centralized assignment system. Performance Bias: (low) double-blind by matching SQ administration device and initial solution volume. Detection Bias: (low) outcomes were adjudicated by separate committees who were blinded to study assignment. Attrition Bias: (high) high rates of attrition in both groups (25-29%). mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were reported appropriately. **Applicability**: Patient: all patients had a history of ACS. 90% on concomitant diabetes medications (metformin, 64%; sulfonylurea, 31%). Intervention: appropriate dose of lixisenatide used. Comparator: placebo comparison appropriate. Outcomes: composite of major cardiac events is an outcome required by the FDA to ensure new antidiabetic therapy is not associated with unacceptable levels of cardiac risk. Composite outcome driven by nonfatal MI events (61.9% in the placebo group and 62.8% in the lixisenatide group) Setting: forty-nine countries, 23% of patients were studied at US study sites.

Abbreviations [alphabetic al order]: ACS = acute coronary syndrome; ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; ITT = intention to treat; LSMD = least squares mean difference; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PP = per protocol; SC = subcutaneous; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

* Symptomatic hypoglycemia defined as having symptoms consistent with hypoglycemia with a blood glucose <60 mg/dL or if no glucose measurement was done then prompt recovery after carbohydrate or glucose administration.

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Appendix 1: Current Status on Preferred Drug List

GLP-1 RECEPTOR AGONISTS

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-CUT	PEN INJCTR	BYETTA	EXENATIDE	Y
SUB-CUT	PEN INJCTR	VICTOZA 3-PAK	LIRAGLUTIDE	N
SUB-CUT	VIAL	BYDUREON	EXENATIDE MICROSPHERES	N
SUB-CUT	PEN INJCTR	BYDUREON PEN	EXENATIDE MICROSPHERES	N
SUB-CUT	PEN INJCTR	TANZEUM	ALBIGLUTIDE	N
SUB-CUT	PEN INJCTR	TRULICITY	DULAGLUTIDE	N

Appendix 2: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADLYXIN safely and effectively. See full prescribing information for ADLYXIN.

ADLYXIN (lixisenatide) injection, for subcutaneous use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------

ADLYXIN is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

Limitations of Use (1):

- Has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not for treatment of type 1 diabetes or diabetic ketoacidosis.
- Has not been studied in combination with short acting insulin.
- Has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.

----------DOSAGE AND ADMINISTRATION----------

- Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20 mcg once daily (2.1).
- Administer once daily within one hour before the first meal of the day (2.2).
- Inject subcutaneously in the abdomen, thigh or upper arm (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 50 mcg/mL in 3 mL in green prefilled pen (for 14 pre-set doses; 10 mcg per dose) (3).
- Injection: 100 mcg/mL in 3 mL in burgundy prefilled pen (for 14 pre-set doses; 20 mcg per dose) (3).

----------CONTRAINDICATIONS----------

Hypersensitivity to ADLYXIN or any product components. Hypersensitivity reactions including anaphylaxis have occurred with ADLYXIN (4).

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis and Serious Hypersensitivity Reactions: Discontinue ADLYXIN and promptly seek medical advice (5.1).
- Pancreatitis: Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis (5.2).
- Never share ADLYXIN pen between patients, even if the needle is changed (5.3).
- Hypoglycemia with Concomitant use of Sulfonylurea or Basal Insulin: When ADLYXIN is used with a sulfonylurea or basal insulin, consider lowering the dose of the sulfonylurea or basal insulin to reduce the risk of hypoglycemia. (5.4).
- Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. ADLYXIN is not recommended in patients with end stage renal disease (5.5).
- Immunogenicity: Patients may develop antibodies to lixisenatide. If there is worsening glycemic control or failure to achieve targeted glycemic control, significant injection site reactions or allergic reactions, alternative antidiabetic therapy should be considered (5.6).
- Macrovascular Outcomes: Clinical studies have not shown macrovascular risk reduction with ADLYXIN or any other antidiabetic drug (5.7).

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥5%) of patients treated with ADLYXIN are nausea, vomiting, headache, diarrhea, dizziness, and hypoglycemia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- ADLYXIN delays gastric emptying which may impact absorption of concomitantly administered oral medications. Oral medications that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, or medications for which a delay in effect is undesirable, such as acetaminophen, should be administered 1 hour before ADLYXIN (7.1, 12.3).
- Oral contraceptives should be taken at least 1 hour before ADLYXIN administration or 11 hours after the dose of ADLYXIN (7.1, 12.3).

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: ADLYXIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2016

Appendix 3: Prior Authorization Criteria

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All GLP-1 receptor agonists

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	**Yes: Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

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P&T Review: *11/16 (KS); 9/16 (KS); 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *2/15; 1/14*