Brand Name: Adlyxin

Generic Name: lixisenatide

Manufacturer: Sanofi-Aventis U.S. LLC[1]

Drug Class: Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist[2,3,4]

Uses:

Labeled Uses[1,2,3,4,5]: Type 2 diabetes mellitus

Unlabeled Uses[4]: none

Mechanism of Action[1,2,4,5]:

Lixisenatide is a GLP-1 receptor agonist that helps to control blood glucose levels in multiple ways. It enhances glucose-dependent insulin secretion, slows gastric emptying, decreases glucagon secretion, promotes beta-cell proliferation, and reduces food intake.

Pharmacokinetics[1,2,3,4,5]:

T_{max}	1-3.5 hours
V_d	100 L
$t_{1/2}$	3 hours
Clearance	35 L/hour
Protein Binding	Not Reported
Bioavailability	Not Reported

Metabolism: Lixisenatide is eliminated through glomerular filtration and proteolytic degradation.

Elimination: No data reported.

Efficacy[6,7,8]:

Rosenstock J, Raccah D, Korányi L, Maffei L, Boka G, Miossec P, Gerich JE. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care. 2013;36(10):2945-51.

Study Design: Randomized, parallel-group, open-label, multicenter, multinational, non-inferiority study

Description of Study: *Methods:* Six-hundred-thirty-nine patients were randomized 1:1 to receive either lixisenatide once daily, titrated to 20mcg or exenatide twice daily, titrated to 10mcg. Inclusion criteria consisted of: participants aged 21-84 years, type 2 diabetes diagnosis, taking at least 1.5 g/day of metformin, and an HbA_{1C} 53-86 mmol/mol (7-10%). The primary endpoint was the absolute change in HbA_{1C} from baseline to week 24. The predefined noninferiority margin is 0.4%. *Outcome Results:* Lixisenatide once daily was non-inferior to exenatide twice daily, in terms of HbA_{1C} reduction from baseline to week 24. Mean ± SD HbA_{1C} decreased from 7.97 ± 0.82% to 7.17 ± 0.96% and from 7.96 ± 0.77% to 7.01 ± 0.88% for lixisenatide and exenatide, respectively. The least squares mean change difference between the two groups was 0.17% (95%

CI, 0.033-0.297). The overall rates of adverse events were similar between lixisenatide and exenatide. Gastrointestinal (GI) events and symptomatic hypoglycemia were less frequent in the lixisenatide group than the exenatide group, with significantly less participants reporting nausea (24.5 vs 35.1%, respectively; P <0.05 and 2.5 vs 7.9%, respectively; P <0.05).

Limitations: This study was sponsored by Sanofi, the manufacturer of lixisenatide, and several authors were employed or affiliated with the company. 93% of the patients in this study were Caucasian, making it hard to generalize these results to the rest of the population. The dosing for metformin was not consistent in all patients, which could have influenced the reduction in HbA_{1C}. The open label study design could bias the study results seen. Diet and exercise were not addressed in the study, which could have led to bias, especially with the open-label design.

Conclusion: While this study was promising, further research is needed to solidify the placement of lixisenatide in current diabetes therapy. Blinded studies with diverse demographics, and consistent metformin dosing are required.

Bolli GB, Munteanu M, Dotsenko S, Niemoeller E, Boka G, Wu Y, Hanefeld M. Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). Diabet Med. 2014;31(2):176-84.

Study Design: Randomized, double-blind, placebo-controlled, four-arm, parallel-group, multicenter, multinational study

Description of Study: *Methods:* Four-hundred-eighty-four patients were randomized 2:2:1:1 to receive lixisenatide one-step dose increase (10 mcg once daily for two weeks, then 20 mcg once daily; n=161), lixisenatide two-step dose increase (10 mcg daily for one week, 15 mcg daily for one week, then 20 mcg once daily; n=161), placebo matching the one-step dose increase (n=82), or placebo matching the two-step dose increase (n=80). There was a double-blind treatment period of 24 weeks, followed by a variable, double-blind extension period of at least 52 weeks. Inclusion criteria consisted of: participants aged 24-79 years, Type 2 diabetes diagnosis for at least a year, taking at least 1.5 g/day of metformin for at least three months as monotherapy, and an HbA_{1C} 53-86 mmol/mol (7-10%). The primary endpoint was the absolute change in HbA_{1C} from baseline to week 24. *Outcome Results:* Mean (± SD) HbA_{1C} was reduced from 64 ± 9.6 mmol/mol and 65 ± 9.7 mmol/mol at week 24 to 54 ± 9.3 mmol/mol and 56 ± 10.9 mmol/mol with lixisenatide one step and lixisenatide two step, respectively. The least squares mean change difference vs. placebo was –5 mmol/mol (95% CI –7.3 to –3.5 mmol/mol; P < 0.0001) for lixisenatide one-step and –5 mmol/mol (95% CI –6.4 to –2.5 mmol/mol; P < 0.0001) for lixisenatide two-step. The study showed a trend toward lower levels of GI side effects, with the most common side effects being mild or moderate nausea and vomiting.

Limitations: This study was sponsored by Sanofi, the manufacturer of lixisenatide, and six of the seven authors are affiliated with the company. 88% of the patients in this study were Caucasian, making it hard to generalize these results to the rest of the population. Another limitation is the dosing for metformin was not consistent in all patients, which could have influenced the reduction in HbA_{1C}.

Conclusion: This study showed that the addition of the once-daily GLP-1 receptor agonist lixisenatide, when used in either a one- or two-step dose increase regimen, significantly improved glycemic control in patients with Type 2 diabetes, not controlled on metformin alone. The possibility of once daily lixisenatide as a one-step dose increase monotherapy agent was

supported by the data. More studies are needed to solidify the role of lixisenatide as a monotherapy option.

Meier JJ, Rosenstock J, Hincelin-Méry A, Roy-Duval C, Delfolie A, Coester HV, Menge BA, Forst T, Kapitza C. Contrasting Effects of Lixisenatide and Liraglutide on Postprandial Glycemic Control, Gastric Emptying, and Safety Parameters in Patients With Type 2 Diabetes on Optimized Insulin Glargine With or Without Metformin: A Randomized, Open-Label Trial. Diabetes Care. 2015 Jul;38(7):1263-73.

Study Design: Multicenter, randomized, open-label, three-arm trial

Description of Study: *Methods:* One-hundred-forty-two patients were randomized 1:1:1 to receive lixisenatide 20 mcg s.c. once daily, liraglutide 1.2 mg s.c. once daily, or liraglutide 1.8 mg s.c. once daily as add-on therapy to optimized insulin glargine for eight weeks. There was an 8-week treatment period with pharmacodynamics assessment at the end of treatment. There was also a follow-up period with an end-of-study visit 7±2 days after the end of treatment. Inclusion criteria consisted of: participants aged 18-75 years with type 2 diabetes for at least one year, BMI 20.0-40.0 kg/m^2, HbA_{1C} ≥6.5% to ≤9.5%, on NPH or insulin glargine for at least three months at screening (stable dose for 2 months) alone or combined with a stable dose of metformin with/without a DPP-4 inhibitor or sulfonylurea. The primary endpoint was week eight change from baseline in pre-meal adjusted AUC PPG from the start of a standardized breakfast until four hours later. *Outcome Results:* Mean ± SD AUC PPG with lixisenatide 20 mcg declined from 15.76 ± 6.7 h*mmol/L at baseline to 3.5 ± 6.5 h*mmol/L at week eight. Mean ± SD AUC PPG at baseline in the liraglutide 1.2 and 1.8 mg arms was 15.6 ± 5.6 h*mmol/L and 17.0 6 5.7 h*mmol/L, respectively, and treatment resulted in reductions to 9.5 ± 5.3 h*mmol/L and 8.7 ± 3.5 h*mmol/L. Marginal mean [95% one-sided CI] difference for lixisenatide 20 mcg versus liraglutide 1.2 mg was -6.0 h*mmol/L and versus liraglutide 1.8mg was -4.6 h*mmol/L ($P < 0.001$ for both comparisons). GI side effects were reported less frequently with lixisenatide than with both liraglutide groups, with the most common side effects being symptomatic hypoglycemia and nausea.

Limitations: This trial was sponsored by Sanofi, the manufacturer of lixisenatide, and seven of the nine authors are affiliated with the company. The open-label design could have introduced bias into the results. Patients were on varying doses of glargine and metformin, which could affect results independently. Finally, 99% of participants were Caucasian, which limits the use for the general population.

Conclusion: This trial did have promising results for lixisenatide's ability to decrease pre-meal AUC, however, more studies are needed to solidify its place in current diabetes therapy. Double-blind studies that have a more varied demographic and a better control of other diabetes medications are required.

Contraindications[1,2,3,4,5]:

Hypersensitivity: Lixisenatide is contraindicated in patients with a documented hypersensitivity to lixisenatide, or any of its components. Caution should be used in patients with severe hypersensitivity to other GLP-1 agonists because it is not known if a cross-sensitivity is possible.

Precautions[1,2,3,4,5]:

Anaphylaxis and Serious Hypersensitivity Reactions: In clinical trials, there were cases of anaphylaxis and other hypersensitivity reactions (i.e., angioedema). Patients with a history of these reactions to any GLP-1 agonist should be closely monitored for allergic reactions. In the event that a hypersensitivity occurs, the patient should discontinue lixisenatide and seek medical attention.

Pancreatitis: Pancreatitis has been reported in patients utilizing GLP-1 receptor agonists. Use caution in patients with risk factors for pancreatitis (i.e., history of cholelithiasis or alcoholism). After initiation of lixisenatide, observe patients for symptoms of pancreatitis. For suspected pancreatitis, lixisenatide should be discontinued, and if confirmed, it should not be restarted.

Sharing of Adlyxin: Lixisenatide pens are for single patient use only. The pens should NEVER be shared, even if the needle is changed, because there is potential for spread of blood-borne pathogens.

Hypoglycemia and Concomitant Use of Sulfonylurea or Basal Insulin: Taking lixisenatide in combination with sulfonylureas or basal insulin can result in hypoglycemia. Reduction in the dose of insulin or sulfonylurea may be warranted.

Acute Kidney Injury: Acute kidney injury or worsening of renal failure have been reported. Monitor renal function when starting or changing the dose of lixisenatide. *Note: Lixisenatide is not recommended for patients with end stage renal disease.

Immunogenicity: Patients taking lixisenatide may develop antibodies after therapy has been initiated. If glycemic control is not achieved or the patient experiences significant allergic reactions, alternative therapy may be necessary.

Macrovascular Outcomes: Macrovascular risk reduction has not been showed with lixisenatide, or any other diabetic medication.

Gastroparesis: Lixisenatide use is not recommended in patients with gastroparesis. Lixisenatide slows gastric emptying and can exacerbate preexisting gastroparesis.

Lactation: Lixisenatide excretion into breast milk is unknown at this time.

Pregnancy: There is not yet sufficient data to determine if lixisenatide is safe to use during pregnancy.

Pediatrics: The safety and efficacy of lixisenatide has not yet been studied in children under 18 years old.

Adverse Events[1,2,4]:

Occurring in <10% of patients (common)
- *Gastrointestinal*
  - Nausea (25%)
  - Vomiting (10%)

Occurring in <1% to <10% of patients (infrequent)
- *Endocrine/Metabolic*
  - Hypoglycemia (2%)

Gastrointestinal
Dyspepsia (3.2%)
Diarrhea (8%)
Constipation (2.8%)
Abdominal Pain (2.2%)
Neurologic
Dizziness (7%)
Headache (9%)
Immunologic
Injection Site Reaction (4%)
Antibody Formation (2.4%)

Occurring in <1% of patients (rare)
Gastrointestinal
Pancreatitis - *Severe
Immunologic
Anaphylactoid - *Severe
Urticaria

Occurring in an unknown number of patients
Respiratory
Bronchospasm - *Severe
Laryngeal Edema - *Severe
Cardiac
Hypotension
Immunologic
Pruritus
Renal
Renal Failure (unspecified) - *Severe

Drug Interactions[1,2,3,4,5]:

Alpha-Lipoic Acid
May enhance the hypoglycemic effect of Antidiabetic Agents

Androgens
May enhance the hypoglycemic effect of Blood Glucose Lowering Agents. Exceptions: Danazol.

Contraceptives (Estrogens)
Lixisenatide may decrease the serum concentration of Contraceptives (Estrogens). Management: Administer oral contraceptives 1 hour before or at least 11 hours after administration of lixisenatide.

Contraceptives (Progestins)
Lixisenatide may decrease the serum concentration of Contraceptives (Progestins). Management: Administer oral contraceptives 1 hour before or at least 11 hours after administration of lixisenatide.

Hyperglycemia-Associated Agents
May diminish the therapeutic effect of Antidiabetic Agents.

Hypoglycemia-Associated Agents
Antidiabetic Agents may enhance the hypoglycemic effect of Hypoglycemia-Associated Agents.

Insulin

GLP-1 Agonists may enhance the hypoglycemic effect of Insulin. Management: Consider insulin dose reductions when used in combination with glucagon-like peptide-1 agonists. Avoid the use of lixisenatide in patients receiving both basal insulin and a sulfonylurea.

MAO Inhibitors

May enhance the hypoglycemic effect of Blood Glucose Lowering Agents.

Pegvisomant

May enhance the hypoglycemic effect of Blood Glucose Lowering Agents.

Quinolone Antibiotics

May enhance the hypoglycemic effect of Blood Glucose Lowering Agents. Quinolone Antibiotics may diminish the therapeutic effect of Blood Glucose Lowering Agents. Specifically, if an agent is being used to treat diabetes, loss of blood sugar control may occur with quinolone use.

Salicylates

May enhance the hypoglycemic effect of Blood Glucose Lowering Agents.

Selective Serotonin Reuptake Inhibitors

May enhance the hypoglycemic effect of Blood Glucose Lowering Agents.

Sulfonylureas

GLP-1 Agonists may enhance the hypoglycemic effect of Sulfonylureas. Management: Consider sulfonylurea dose reductions when used in combination with glucagon-like peptide-1 agonists. Avoid the use of lixisenatide in patients receiving both basal insulin and a sulfonylurea.

Thiazide and Thiazide-Like Diuretics

May diminish the therapeutic effect of Antidiabetic Agents.

Dosing/Administration[1,2,3,4,5]:

Adult Dosing

Initially: 10 mcg subcutaneously within one hour before breakfast. Injection should be given subcutaneously in the abdomen, thigh, or upper arm. Continue 10 mcg once daily for 14 days.

Maintenance: Starting on day 15, increase the dose to 20 mcg subcutaneously once daily.

Pediatric Dosing

The safety and efficacy of lixisenatide has not been proven in children under the age of 18 years old.

Geriatric Dosing

No overall differences were found in the clinical trials between adult patients and geriatric patients; however, this does not mean that individual sensitivities do not exist.

Hepatic Impairment

No dose adjustments are necessary.

Renal Impairment

Mild renal impairment (eGFR 60-89 mL/min/1.73m^2): no dose adjustment is necessary

Moderate renal impairment (eGFR 15-<60 mL/min/1.73m^2): no current recommendations

End Stage Renal Disease (eGFR <15 mL/min/1.73m^2): use is not recommended

Use in Special Circumstances[1,2,3,4,5]:

Pregnancy

The data is not sufficient to identify a drug-associated risk to the mother and/or the fetus; however, there are risks to both the mother and the fetus associated with uncontrolled diabetes during pregnancy. Lixisenatide should only be used if the potential benefits outweigh the potential risks.

Lactation

There have been no studies done to measure the presence of lixisenatide in human milk; however, it is present in rat milk.

Conclusion:

Lixisenatide is a safe and effective adjunct therapy for patients with type 2 diabetes not well controlled on metformin. Lixisenatide is safe for use with metformin and glargine (basal) insulin, but more research is needed to determine safety and efficacy with other diabetes therapy combinations. Adverse events occur less frequently than with exenatide and liraglutide. With its tolerability, minimal drug interactions, and effectiveness in decreasing HbA_{1C} and AUC in patients with Type 2 diabetes, lixisenatide appears to be another clinically useful antidiabetic agent, and further studies will help to solidify its placement in therapy.

Recommended References:

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2. Lixisenatide. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2009. Available at: http://www.clinicalpharmacology.com Accessed: August 12, 2016.
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5. Lixisenatide Injection. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: August 12, 2016.
6. Rosenstock J, Raccah D, Korányi L, Maffei L, Boka G, Miossec P, Gerich JE. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care. 2013;36(10):2945-51.
7. Bolli GB, Munteanu M, Dotsenko S, Niemoeller E, Boka G, Wu Y, Hanefeld M. Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). Diabet Med. 2014;31(2):176-84.
8. Meier JJ, Rosenstock J, Hincelin-Méry A, Roy-Duval C, Delfolie A, Coester HV, et.al. Contrasting Effects of Lixisenatide and Liraglutide on Postprandial Glycemic Control, Gastric Emptying, and Safety Parameters in Patients With Type 2 Diabetes on Optimized Insulin Glargine With or Without Metformin: A Randomized, Open-Label Trial. Diabetes Care. 2015 Jul;38(7):1263-73.

Prepared by: Tamra L. Little, Doctor of Pharmacy Candidate