Drug Monograph

Drug/Drug Class:	**Adlyxin® (lixisenatide) solution for injection/ GLP-1 Agonist**
Prepared for:	MO HealthNet
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☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Adlyxin® is available in two different strengths of prefilled pens in 3 ml solution. It is available in a 50 mcg/ml prefilled pen that contains 10 mcg/dose, and it is also available in a 100 mcg/ml prefilled pen that contains 20 mcg/dose. Manufacturer: Sanofi-Aventis U.S. LLC, Bridgewater, NJ 08807
Summary of Findings:	Adlyxin® demonstrates significant improvements in HbA1c compared with placebo in patients with type 2 diabetes. As monotherapy, a reduction in HbA1c of 0.77% to 0.94% with Adlyxin® was superior to placebo (-0.27%) in a 12-week study. HbA1c reductions of 0.57% to 0.91% occurred with Adlyxin® when used as add-on therapy in 6 month studies with metformin with or without sulfonylureas. As add-on therapy, Adlyxin® was noninferior to exenatide in improving HbA1c levels in one trial and noninferior to insulin glulisine once daily in a second trial, but Adlyxin® provided significantly less HbA1c reduction compared with insulin glulisine given 3 times daily (-0.57% vs. -0.8%).
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [8]

Approximately 21 million people in the United States have been diagnosed with diabetes according to the Centers for Disease Control and Prevention. Over time, diabetes increases the risk of serious health complications, including heart disease, blindness, nerve and kidney damage. Improvement in blood sugar control can reduce the risk of some of these long-term complications.

Dosage Form(s) [1]

Adlyxin® is available in two different strengths of prefilled pens in 3 ml solution. It is available in a 50 mcg/ml prefilled pen that contains 10 mcg/dose, and it is also available in a 100 mcg/ml prefilled pen that contains 20 mcg/dose

Manufacturer [1]

Sanofi-Aventis U.S. LLC, Bridgewater, NJ 08807

Indication(s) [1]

Adlyxin® is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Clinical Efficacy [1,2,3,4,5,6,7] (mechanism of action/pharmacology, comparative efficacy)

Adlyxin® is a GLP-1 receptor agonist that enhances glucose-dependent insulin release, decreases glucagon secretion, and slow gastric emptying.

Pharmacokinetics:

	Adlyxin®
Metabolism	Proteolytic degradation
Excretion	Urine
Half-life	3 hours
Volume of distribution	100 L

Study 1

Lixisenatide monotherapy was superior to placebo in improving HbA1c values among patient with type 2 diabetes

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 12 week trial (n=361).
INCLUSION CRITERIA	Adults 20 years and older with type 2 diabetes not currently receiving glucose-lowering therapy and with HbA1c values between 7% and 10%.
EXCLUSION CRITERIA	Patients who received a glucose-lowering agent within the previous 3 months.
TREATMENT REGIMEN	Patients were randomized to receive monotherapy with placebo or Adlyxin® administered according to 2 different titration schedules: 1) 10 mcg subQ once daily for 1 week, then 15 mcg once daily for 1 week, then 20 mcg once daily, or 2) 10 mcg once daily for 2 weeks, then 20 mcg once daily.
RESULTS	Monotherapy with Adlyxin® significantly reduced HbA1c compared with placebo (-0.77% and -0.94% with Adlyxin® vs. -0.27%) from a mean baseline HbA1c of 8%. An HbA1c of less than 7% was reached by 52.2% and 46.5% of patients receiving Adlyxin® compared with 26.8% receiving placebo.
SAFETY	Gastrointestinal events were the most common, with nausea occurring in 23% and 4.1% of patients receiving Adlyxin® and placebo, respectively. Symptomatic hypoglycemia occurred in 1.7% and 1.6% of patients, respectively, but no severe cases were reported.

Study 2

Lixisenatide was noninferior to exenatide in lowering HbA1c levels after 24 weeks of treatment when used as add-on therapy to metformin.

STUDY DESIGN	Randomized, 24-week, phase 3, noninferiority trial (N=639).
INCLUSION CRITERIA	Adults 21 years and older with type 2 diabetes inadequately controlled with metformin.
EXCLUSION CRITERIA	Patients who received a glucose-lowering agent other than metformin within the previous 3 months.
TREATMENT REGIMEN	Patients were randomized to receive add-on therapy with Adlyxin® 20 mcg subQ once daily (titrated from 10 mcg once daily for 1 week, then 15 mcg once daily for 1 week, then 20 mcg once daily) or exenatide 10 mcg subQ twice daily (titrated from 5 mcg twice daily).
RESULTS	Hb1Ac reduction with Adlyxin® plus metformin (-0.79%) was noninferior to that of exenatide plus metformin (-0.96%). An HbA1c of less than 7% was obtained by a similar proportion of patients in each treatment group

	(48.5% vs. 49.8%). Weight reduction at 24 weeks was similar with Adlyxin® (-2.96 kg) and exenatide (-3.98 kg).
SAFETY	Adlyxin® was associated with significantly lower rates of symptomatic hypoglycemia (2.5% vs. 7.9%) and nausea (24.5% vs. 35.1%) compared with exenatide.

Contraindications [(1)]

- Hypersensitivity to lixisenatide or any component of the product

Warnings and Precautions [(1)]

- Increased risk of hypoglycemia with concomitant basal insulin or sulfonylurea use; dose reduction of concomitant medication may be warranted.
- Use not recommended in patients with gastroparesis.
- Pancreatitis, including acute pancreatitis (eg, fatal and nonfatal hemorrhagic or necrotizing pancreatitis), has been reported with GLP-1 receptor agonists; monitoring recommended and discontinue use if suspected; if confirmed, do not restart therapy.
- Use not recommended in patients with a history of pancreatitis.
- Anaphylaxis and other serious hypersensitivity reactions (eg, angioedema) have occurred; monitoring recommended and therapy discontinuation required.
- Antibodies to lixisenatide may develop; alternative antidiabetic therapy may be required.
- Antibody-positive patients may have an attenuated glycemic response and a higher risk of allergic reactions and injection site reactions; alternative antidiabetic therapy may be required.
- Use not recommended in patients with end stage renal disease.
- Acute kidney injury and worsening of chronic renal failure, sometimes requiring hemodialysis, have been reported with GLP-1 receptor agonists, and may occur in patients without underlying renal disease; monitoring recommended.
- Never share pens among patients, as transmission of blood-borne pathogens may occur even if the needle is changed.

Adverse Effects [(1)]

Most common, ≥ 5 %	**Adlyxin® (n=2869)**	**Placebo (n=1639)**
Nausea	25%	6%
Vomiting	10%	2%
Headache	9%	6%
Diarrhea	8%	6%
Dizziness	7%	4%

Drug Interactions [1]

- Acetaminophen
- Antibiotics
- Insulin
- Oral contraceptives
- Sulfonylureas

Dosage and Administration [1]

The FDA recommended dose is 10 mcg subcutaneously into the abdomen, thigh, or upper arm once daily for 14 days, then increase to 20 mcg once daily starting on day 15. Administer within one hour before the first meal of the day.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	Dose	COST/ UNIT*
Lixisenatide	Adlyxin	Sanofi-Aventis	50 mcg/ml, 3 ml prefilled syringe	20 mcg once daily	$278.58
			100 mcg/ml, 3 ml prefilled syringe	20 mcg once daily	$278.58
Dulaglutide	Trulicity	Eli Lilly	0.75 mg/0.5 ml single-dose pen	0.75 mg once weekly	$244.16
			1.5 mg/0.5 ml single-dose pen	1.5 mg once weekly	$244.16

*Wholesale Acquisition Cost

Conclusion

Adlyxin® is a once daily subcutaneous GLP-1 receptor agonist approved for the treatment of type 2 diabetes as an adjunct to diet and exercise. Adlyxin® demonstrated efficacy with HbA1c reductions ranging from 0.57% to 0.91% when used as monotherapy and in combination with various other antidiabetic agents. When used as add-on therapy in clinical trials, Adlyxin® was noninferior to exenatide. A large clinical trial found no risk reduction in cardiovascular outcomes with Adlyxin®. Gastrointestinal adverse effects account for the most commonly reported toxicity. Adlyxin® is not recommended for type 1 diabetes mellitus, diabetic ketoacidosis, or patients with gastroparesis or a history of pancreatitis, and has not been studied with short-acting insulin.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1) Product Information: Adlyxin™, lixisenatide injection. Sanofi-Aventis US LLC, Bridgewater, NJ, 07/2016.

2) Fonseca VA, Alvarado-Ruiz R, Raccah D et al: Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). Diabetes Care 2012; 35(6):1225-1231.
3) Rosenstock J, Raccah D, Koranyi L et al: 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):2945-2951.
4) Rosenstock J, Hanefeld M, Shamanna P et al: Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S). J Diabetes Complications 2014; 28(3):386-392.
5) Pinget M, Goldenberg R, Niemoeller E et al: Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). Diabetes Obes Metab 2013; 15(11):1000-1007.
6) Rosenstock J, Guerci B, Hanefeld M et al: Prandial options to advance basal insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: the GetGoal Duo-2 Trial. Diabetes Care 2016; 39(8):1318-1328.
7) Pfeffer MA, Claggett B, Diaz R et al: Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015; 373(23):2247-2257.
8) FDA approves two new drug treatments for diabetes mellitus. Retrieved 01/20/16 from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm464321.htm

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