

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists
Drug Class Review
68:20.06 Incretin Mimetics

Exenatide (Byetta®, Bydureon®)
Liraglutide (Victoza®)

Final Report
May 2013

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Executive Summary

Introduction: Three Glucagon-like Peptide-1 (GLP-1) Receptor Agonists are currently available for use in the United States: exenatide (Byetta®), exenatide extended release (Bydureon®) and liraglutide (Victoza®). GLP-1 is a hormone released in the gastrointestinal tract after meals which stimulates insulin secretion, inhibits glucagon release, delays gastric emptying, reduces food intake, and normalizes fasting and postprandial insulin secretion. The GLP-1 agonists mimic these effects. The GLP-1 receptor agonists are administered subcutaneously and are indicated in the treatment of type 2 diabetes mellitus. Byetta® is administered twice daily before meals, Bydureon® is administered once weekly with or without food, and Victoza® is administered once daily with or without food.

Diabetes mellitus (DM) is a broad term describing metabolic disorders associated with hyperglycemia. An estimated 300 million people worldwide have DM and it is listed as the seventh leading cause of death. The prevalence of DM increases with age, is similar across genders, varies across different ethnic populations and continues to be a leading cause of morbidity and mortality across the world. Treatment of type 2 DM may include a combination of antidiabetic agents in addition to therapies to treat other comorbid conditions associated with DM. The American Diabetes Association Standards of Medical Care in Diabetes (2013) recommends metformin as the preferred first-line agent for treatment of type 2 diabetes. A GLP-1 receptor agonist may be added to a patient's regimen if metformin monotherapy is contraindicated, not tolerated or does not achieve the target A1C at 3-6 months. Choice of diabetes treatment should be based on individual patient characteristics.

Clinical Efficacy: The efficacy of GLP-1 receptor agonists was directly compared in one meta-analysis and four clinical trials. The evidence suggests both exenatide and liraglutide are efficacious in reducing A1C in patients with type 2 DM. Liraglutide therapy may be more efficacious in reducing A1C, fasting blood glucose, and weight than exenatide therapy and exenatide therapy may be more efficacious in reducing post-prandial blood glucose levels than liraglutide therapy. Higher rates of gastrointestinal adverse events were reported with liraglutide treatment while higher rates of injection site reactions were reported with exenatide once weekly treatment. Overall ranges of A1C reduction seen with exenatide, exenatide ER, and liraglutide in current literature are similar.

Special Populations: No differences in safety or efficacy were found in Asian patients or in patients of older age.

Adverse Drug Reactions: The most common drug-related adverse reactions associated with the GLP-1 receptor agonists are gastrointestinal disturbances. Nausea and vomiting associated with the GLP-1 agonists are dose-dependent and appear to decrease over time. The GLP-1 receptor agonists have a boxed warning regarding dose and duration dependent thyroid C-cell tumors occurring in animal studies. A new alert from The Food and Drug Administration (FDA) warns of an association between GLP-1 agonist treatment with pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis.

Summary: The GLP-1 receptor agonists are indicated in the treatment of type 2 diabetes mellitus and may be considered second-line or add-on therapy in patients where metformin monotherapy is contraindicated, not tolerated or does not achieve the target A1C. The evidence suggests both exenatide and liraglutide are efficacious in reducing A1C in patients with type 2 DM. Liraglutide therapy may be more efficacious in reducing A1C while exenatide therapy may be more efficacious in improving post-prandial blood glucose levels. Gastrointestinal disturbances are the most common reported adverse events with GLP-1 agonist treatment. In clinical trials, higher rates of gastrointestinal adverse events were reported with liraglutide treatment while higher rates of injection site reactions were reported with exenatide once weekly treatment.

Introduction

Several diabetes therapies are currently available for use in the United States including: sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides and incretin-based therapies (dipeptidyl peptidase IV (DPP-IV) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists).^{1,2} Table 2 provides a summary of the antidiabetic drug classes. This review will focus on the glucagon-like peptide-1 (GLP-1) receptor agonists. Three medications are included in the GLP-1 receptor agonist drug class: exenatide (Byetta®), exenatide extended release (Bydureon®) and liraglutide (Victoza®).³⁻⁵ Table 1 compares these agents. The GLP-1 receptor agonists are administered subcutaneously and are indicated in the treatment of type 2 diabetes mellitus.^{1,2}

Table 1. Comparison of the Glucagon-like Peptide-1 (GLP-1) Receptor Agonists¹⁻⁵

Agents	Available doses	Indications	Dose range	Clinical features	Generic
Exenatide (Byetta®, Bydureon®) <i>Amylin</i>	Injection, solution (Byetta®): 250 mcg/mL (2.4 mL) [10 mcg/0.04 mL; 60 doses] 250 mcg/mL (1.2 mL) [5 mcg/0.02 mL; 60 doses]	Treatment of type 2 diabetes mellitus (noninsulin dependent, NIDDM) to improve glycemic control	Immediate release: 5-10 mcg twice daily 60 minutes prior to a meal	Byetta® is supplied in a pre- mixed pen Byetta® must be given 60 minutes prior to a meal	Not available
	Injection solution, extended release (Bydureon®): 2 mg [contains polylactide- co-glycolide, sucrose 0.8 mg/vial; supplied with diluent]		Extended release: 2 mg once weekly	Bydureon® must be reconstituted by the patient Bydureon® has a smaller gauge needle Bydureon® may be given without regard to food	
Liraglutide (Victoza®) <i>Novo Nordisk</i>	Injection, solution: 6 mg/mL (3 mL) [contains propylene glycol 14 mg/3 mL]	Treatment of type 2 diabetes mellitus (noninsulin dependent, NIDDM) to improve glycemic control	0.6 mg once daily for 1 week; then increase to 1.2-1.8 mg once daily	Supplied in a pre-mixed pen May be given without regard to food	Not available

Disease Overview

Diabetes mellitus (DM) is broad term describing metabolic disorders associated with hyperglycemia.^{6,7} In 2010, an estimated 300 million people worldwide had DM compared to 30 million cases in 1985. This number is expected to continue to rise and the International Diabetes Federation estimates 438 million individuals will have diabetes by the year 2030. In the United States (US), the Centers for Disease Control and Prevention (CDC) estimated over 25 million

people had diabetes in 2010 (~8.3% of the population) and DM was the seventh leading cause of death in 2007. DM is also the leading cause of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, blindness, and cardiovascular diseases in the US. A recent study suggests diabetes is the fifth leading cause of death worldwide and responsible for almost 4 million deaths in 2010. The prevalence of DM increases with age, is similar across genders, varies across different ethnic populations and will continue to be a leading cause of morbidity and mortality across the world.^{6,7}

Diabetes mellitus is a metabolic disorder associated with hyperglycemia as a result of insulin deficiency, reduced insulin secretion, and/or increased glucose production.^{6,7} Two categories of DM are type 1 and type 2 and are classified based on the pathogenic process that leads to hyperglycemia. Both types are associated with a complex combination of genetics and environmental factors and begin with abnormal glucose homeostasis. A severe or total insulin deficiency follows in type 1 DM. In type 2 DM, varying degrees of insulin resistance, impaired insulin secretion, and increased glucose production follows the initial glucose imbalance. The defects in insulin action in type 2 DM provide important potential therapeutic implications and pharmacologic agents are available to target these specific metabolic disorders. DM may cause secondary pathophysiologic changes in many organ systems including the renal, neurological, cardiovascular and ocular systems. Diabetes mellitus is a chronic disease which places a huge burden on both the patient and on the health care system as a whole.^{6,7}

Treatment of DM varies depending on the clinical subset of DM present and individual patient characteristics.⁶⁻⁸ For type 2 DM, treatment may include a combination of the agents available for use in the United States (sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides and incretin-based therapies) in addition to therapies to treat other comorbid conditions associated with DM (ace inhibitors, HMG-CoA reductase inhibitors (statins), low-dose aspirin, etc.). The two main goals of DM treatment are to eliminate symptoms and reduce microvascular and macrovascular complications associated with chronic hyperglycemia. The American Diabetes Association Standards of Medical Care in Diabetes (2013) recommends metformin as the preferred first-line agent for treatment of type 2 diabetes. In patients with significantly elevated blood glucose levels or A1C level, insulin therapy maybe the preferred first-line agent. If metformin monotherapy is contraindicated, not tolerated or does not achieve the target A1C at 3-6 months, a second agent (sulfonylurea, thiazolidinedione, incretin-based therapy or insulin) may be added. Choice of pharmacological agents should be based on individual patient characteristics, including: efficacy, cost, potential adverse effects, comorbidities, risk of hypoglycemia, and patient preference.⁶⁻⁸

The glucagon-like peptide-1 (GLP-1) receptor agonists are incretin-based therapies indicated as subcutaneous therapies in the treatment of type 2 diabetes.¹⁻⁸ GLP-1 is a hormone released in the gastrointestinal tract after meals which stimulates insulin secretion, inhibits glucagon release, delays gastric emptying, reduces food intake, and normalizes fasting and postprandial insulin secretion. Exendin-4 is a naturally occurring reptilian peptide similar to GLP-1 which causes insulin secretion, delayed gastric emptying, and lowered glucagon levels. There are currently three GLP-1 receptor agonists available for use in the U.S. and several others under development. Exenatide is a synthetic exendin-4 analog dosed twice daily 60 minutes prior

to a meal (Byetta®) or once weekly (Bydureon™).^{1-3,5} Liraglutide is a second GLP-1 agonist with a structure very similar to native GLP-1, which is dosed once daily.⁴

Table 2. Comparison of Antidiabetes Agents¹⁻⁷

Class	Agents in class	Route of administration	Mechanism of action	Labeled Indications
Alpha-glucosidase Inhibitors	Acarbose Miglitol	Oral tablets	Competitive inhibitor of pancreatic enzymes, resulting in delayed metabolism of starches and some sugars	Adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes mellitus
Amylin Mimetics	Pramlintide	Injectable solution; subcutaneous	Synthetic analog of human amylin which works by prolonging gastric emptying, reduces postprandial glucagon secretion, and centrally-mediate appetite suppression	Adjunctive treatment with mealtime insulin in type 1 diabetes mellitus Adjunctive treatment with mealtime insulin in type 2 diabetes mellitus, with or without concurrent sulfonylurea and/or metformin
Biguanides	Metformin Metformin/Alogliptin Metformin/Glipizide Metformin/Glyburide Metformin/Linagliptin Metformin/Pioglitazone Metformin/Repaglinide Metformin/Rosiglitazone Metformin/Saxagliptin Metformin/Sitagliptin	Oral tablets	Decreases hepatic glucose production, decreasing intestinal absorption of glucose and improving insulin sensitivity	First-line management of type 2 diabetes mellitus <u>Unlabeled Indications:</u> Gestational diabetes mellitus (GDM); polycystic ovary syndrome (PCOS); prevention of type 2 diabetes mellitus
Dipeptidyl peptidase IV (DPP-IV) Inhibitors	Alogliptin Alogliptin/Metformin Alogliptin/Pioglitazone Linagliptin Linagliptin/Metformin Saxagliptin Saxagliptin/Metformin Sitagliptin Sitagliptin/Metformin Sitagliptin/Simvastatin	Oral tablets	Inhibits dipeptidyl peptidase IV (DPP-IV) enzyme resulting in prolonged active incretin levels resulting in increased insulin synthesis & release and decreased glucagon secretion	Management of type 2 diabetes mellitus as an adjunct to diet and exercise as monotherapy or in combination with other antidiabetic agents
Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists	Exenatide Liraglutide	Injectable solution; subcutaneous	Analogues of the hormone incretin which increase glucose-dependent insulin secretion, decrease inappropriate glucagon secretion, increase B-cell growth/replication, slow gastric emptying, and decrease food intake	Treatment of type 2 diabetes mellitus *May also improve hypertension in patients with diabetes

<u>Insulins</u>	<u>Rapid-acting</u> Aspart: Novolog Gulisine: Apidra Lispro: Humalog <u>Short-acting</u> Regular: Humulin, Humulin R, Novolin <u>Intermediate-acting</u> NPH: Humulin N, Novolin N <u>Intermediate to Long-acting</u> Detemir <u>Long-acting</u> Glargine <u>Combination Products</u> Aspart protamine + Aspart Lispro protamine + Lispro NPH + Regular: Humulin 70/30, Novolin 70/30	Injectable solution; subcutaneous, intravenous	Insulin acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrate, protein, and fats. Target organs for insulin include the liver, skeletal muscle, and adipose tissue	Treatment of type 1 diabetes mellitus and type 2 diabetes mellitus to improve glycemic control
Meglitinides	Nateglinide Repaglinide Repaglinide/Metformin	Oral tablets	Phenylalanine derivatives which stimulate insulin release and reduce postprandial hyperglycemia	Management of type 2 diabetes mellitus as monotherapy or in combination with metformin or a thiazolidinedione
Sulfonylureas	Chlorpropamide Gliclazide Glimepiride Glimepiride/Pioglitazone Glimepiride/Rosiglitazone Glipizide Glipizide/Metformin Glyburide Glyburide/Metformin Tolazamide Tolbutamide	Oral tablets	Stimulates insulin release, reduces glucose output and increases insulin sensitivity	Management of type 2 diabetes mellitus as monotherapy or in combination with metformin or insulin
Thiazolidinediones	Pioglitazone Pioglitazone/Alogliptin Pioglitazone/Glimepiride Pioglitazone/Metformin Rosiglitazone Rosiglitazone/Glimepiride Rosiglitazone/Metformin	Oral tablets	Agonists for peroxisome proliferator-activated receptor-gamma (PPARgamma) which influences the production of a number of gene products involved in glucose and lipid metabolism	Management of type 2 diabetes mellitus as monotherapy or in combination with a sulfonylurea, metformin, or sulfonylurea plus metformin

Pharmacology/Pharmacokinetics

The glucagon-like peptide-1 (GLP-1) receptor agonists function by activating the GLP-1 receptor on cells in the peripheral and central nervous systems and the cardiovascular, renal, hepatic, and gastrointestinal systems.¹⁻⁷ Activation of the GLP-1 receptor initiates signals in the cAMP pathway, GEFs (guanine nucleotide exchange factors), protein kinase enzymes and several other ion channels, resulting in increased insulin production and distribution in a glucose-dependent manner. The GLP-1 receptor agonists are administered subcutaneously once weekly to twice daily, depending on the formulation. Exenatide is rapidly absorbed, reaches peak concentrations in ~2 hours, undergoes little metabolism in the circulation, has a volume of distribution of ~30 L and is cleared by glomerular filtration.⁵ Exenatide extended release reaches peak concentrations within 2 weeks and has a steady-state plasma concentration after 6-7 weeks.^{3,9} Liraglutide reaches peak concentrations in 8-12 hours, has a t_{1/2} of 12-14 hours, and clearance is primarily through the metabolic pathways of large plasma proteins.⁴

Table 3. Pharmacokinetics of the Glucagon-like Peptide-1 (GLP-1) Receptor Agonists¹⁻⁵

Agents	Distribution	Metabolism	Half-life	Time to peak	Excretion
Exenatide (Byetta®, Bydureon®)	Vd: 28.3 L	Minimal systemic metabolism; proteolytic degradation may occur following glomerular filtration	Byetta®: 2.4 hours Bydureon®: ~2 weeks	Byetta®: 2.1 hours Bydureon®: Triphasic: Phase 1: 2-5 hours Phase 2: ~2 weeks Phase 3: ~7 weeks	Urine (majority of dose)
Liraglutide (Victoza®)	Vd: SubQ: ~13 L I.V.: 0.07 L/kg	Endogenously metabolized by dipeptidyl peptidase IV (DPP-IV) and endogenous endopeptidases *metabolism occurs slower than that seen with native GLP-1	~13 hours	8-12 hours	Urine (6%, as metabolites); feces (5%, as metabolites)

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2013), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only comparative clinical trials published in English and indexed on MEDLINE prior to 4/2013, evaluating efficacy of the glucagon-like peptide-1 (GLP-1) receptor agonists with improvement of symptoms (hyperglycemia, A1C level, etc.) as the endpoint are included. Trials evaluating the GLP-1 receptor agonists as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are

included. Trials comparing the agents with placebo or monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as pharmacokinetics¹⁰⁻¹², pharmacodynamics¹³⁻¹⁵ or cost analysis.
- Individual trials comparing the GLP-1 receptor agonists in dose-finding studies¹⁶⁻²² or in healthy volunteers.¹⁰
- Individual clinical trials evaluating the GLP-1 receptor agonists or formulations not currently available in the US²³⁻³⁴ or clinical trials without access to the full article.

Clinical Efficacy

The efficacy of the glucagon-like peptide-1 (GLP-1) receptor agonists was directly compared in one meta-analysis and four clinical trials.³⁵⁻³⁹ The relative A1C reductions and secondary outcomes reported in these trials are presented in Table 4. Overall, the A1C ranges may be considered clinically similar between the three GLP-1 agonists.

Table 4. Ranges of Outcomes Reported in Clinical Trials Evaluating the GLP-1 Receptor Agonists³⁵⁻³⁹

Agents	Mean A1C reductions	Fasting blood glucose reductions	Post-prandial blood glucose reductions	Weight reductions (Kg)
Exenatide (Byetta®)	0.79-1.5	0.6-2.3	exenatide > liraglutide exenatide > exenatide ER	1.4-3.6
Exenatide (Bydureon®)	1.28-1.9	1.4-1.9	exenatide = exenatide ER exenatide > exenatide ER	2.3-3.7
Liraglutide (Victoza®)	1.12-1.48	1.61-2.12	exenatide > liraglutide	3.24-3.57

Two trials comparing exenatide twice daily to exenatide once weekly are available for evaluation. Drucker et al³⁹ compared the exenatide twice daily formulation to the once weekly formulation in 295 patients with type 2 diabetes. All patients experienced a 3-day lead-in period with exenatide twice a day followed by randomization to continued twice daily exenatide treatment or once weekly exenatide treatment for 30 weeks. At the end of the study period, patients in the exenatide once weekly group demonstrated greater reductions in A1C compared to patients in the exenatide twice daily group (-1.9 vs. -1.5; p=0.0023). Blevins et al³⁵ compared the two exenatide formulations in 252 patients with type 2 diabetes in a 24-week study. After 24 weeks, patients in the exenatide once weekly group had greater reductions in A1C than the exenatide twice daily group (-1.6 vs. -0.9; p<0.0001). Both studies also showed greater improvements in fasting blood glucose levels with exenatide once weekly and similar rates of weight reductions between the treatment groups. Similar types of adverse events were reported between treatment groups with higher rates of nausea reported with the exenatide twice daily groups and higher rates of injections site reactions with the exenatide once weekly groups. No

differences in treatment-related discontinuation rates were reported between treatment groups. Overall, this evidence suggests greater A1C reductions, higher rates of injection site reactions and similar rates of weight reductions with exenatide once weekly treatment compared to exenatide twice daily treatment.

A clinical trial funded by *Novo Nordisk* compared liraglutide 1.8 mg once daily injections to exenatide 10 mcg twice daily injections in 464 adult patients for 26 weeks (LEAD-6).³⁷ Patients had to be diagnosed with type 2 diabetes and receive treatment with metformin or a sulfonylurea or both for at least 3 months prior to enrollment. At the end of the study period, liraglutide treatment resulted in greater mean A1C reductions compared to treatment with exenatide (-1.12% vs. -0.79%; $p < 0.0001$). Liraglutide treatment also produced greater improvements in fasting blood glucose levels while exenatide treatment was associated with greater improvements in post-prandial glucose levels. Both treatments demonstrated similar rates of weight reduction. A 14-week extension of the LEAD-6 trial followed patients who switched from exenatide twice daily to liraglutide 1.8 mg daily and found conversion from exenatide to liraglutide resulted in reductions in A1C, fasting blood glucose levels, body weight, and systolic blood pressure values.⁴⁰ Overall, these data suggest liraglutide is efficacious in improving A1C levels in patients with type 2 diabetes. Both trials found similar rates of adverse events between treatment groups. Gastrointestinal dysfunction (nausea, vomiting, constipation, diarrhea, etc.) was the most frequently reported adverse event reported in the trials and rates were similar across treatment groups.

A clinical trial funded by *Amylin* compared exenatide once weekly injections to liraglutide once daily injections in 911 adult patients over 26 weeks (DURATION-6).³⁶ Patients had to have uncontrolled type 2 diabetes despite receiving treatment with a maximum dose of an oral anti-hyperglycemic medication. Mean reductions in A1C were greater in the liraglutide treatment group compared to the exenatide treatment group (-1.48% vs. -1.28%, $p = 0.02$). Greater reductions in weight and improvements in fasting blood glucose levels were reported with the liraglutide group compared to the exenatide group but these results were not statistically significant. Nausea (21% vs. 9%), diarrhea (13% vs. 6%), and vomiting (11% vs. 4%) occurred more frequently in the liraglutide group compared to the exenatide group while injection site reactions occurred more frequently in the exenatide group (10% vs. 1%). Overall, this data suggest liraglutide may be more effective in reducing A1C but may also be associated with higher rates of gastrointestinal adverse events.

A meta-analysis funded by *Amylin* pharmaceuticals reviewed 22 randomized, controlled trials evaluating exenatide, liraglutide, and/or insulin glargine therapy in patients with type 2 diabetes.³⁸ The authors identified trials lasting at least 24 weeks comparing exenatide twice daily, exenatide once weekly, liraglutide (1.2 mg or 1.8 mg), insulin glargine or placebo and estimated probability rankings based on mean differences in HbA1c relative to placebo or each other. Three of the four clinical trials discussed above were included in the probability ranking; the authors excluded the DURATION-6 trial because they claimed the outcomes from this trial were inconsistent.^{35-37, 39} Based on the pooled data of over 11,000 patients (excluding the DURATION-6 trial), the ranking was as follows: liraglutide 1.8 mg > exenatide once weekly > liraglutide 1.2 mg > exenatide once daily. The authors concluded exenatide once weekly and liraglutide (1.2 mg and 1.8 mg) have similar glycemic effects.

Many placebo controlled and/or mixed treatment trials are also available for evaluation of the GLP-1 agonists. One systematic review⁴¹ of incretin-based therapies concluded that exenatide and liraglutide are more efficacious than placebo in lowering A1C and may also produce weight loss. A second meta-analysis⁴² evaluating clinical evidence available for exenatide versus placebo concluded that exenatide demonstrated improvements in A1C, lipid and blood pressure values and can be considered as a good hypoglycemic agent in type-2 diabetic patients but may be associated with increases in nausea, vomiting and hypoglycemia. A third meta-analysis⁴³ assessing the evidence available for all second-line anti-hyperglycemic therapies found GLP-1 receptor agonists produced similar rates of improvement in glycemic control compared to other second-line therapies (sulfonylureas, meglitinides, thiazolidinediones, insulin, etc.) and may have modest benefits in weight loss and reduced risk of hypoglycemia.

In summary, the evidence suggests both exenatide and liraglutide are efficacious in reducing A1C in patients with type 2 DM. Liraglutide therapy may be more efficacious in reducing A1C, fasting blood glucose, and weight than exenatide therapy (both twice daily and once weekly treatment). Exenatide therapy may be more efficacious in reducing post-prandial blood glucose levels than liraglutide therapy. Higher rates of gastrointestinal adverse events were reported with liraglutide treatment while higher rates of injection site reactions were reported with exenatide once weekly treatment. Overall ranges of A1C reduction seen with exenatide, exenatide ER, and liraglutide in current literature are similar.

Special Populations

In clinical trials evaluating exenatide and liraglutide therapy, no difference between younger and older subjects was reported. Use in patients ≥ 75 years is limited.³⁻⁵

In clinical trials evaluating exenatide therapy in Asian patients, similar rates of adverse events and glycemic control were demonstrated.^{44, 45}

Adverse Drug Reactions

Glucagon-like peptide-1 (GLP-1) receptor agonists are relatively well tolerated by patients with type 2 diabetes.¹⁻⁵ The most common drug-related adverse reactions associated with the GLP-1 receptor agonists are gastrointestinal disturbances: nausea, vomiting, diarrhea, and constipation (occurring in up to 44% of patients). Nausea and vomiting associated with the GLP-1 agonists are dose-dependent and appear to decrease over time. In general, doses at which the GLP-1 agonists cause GI side effects are higher than those needed to regulate blood glucose. Risk of hypoglycemia is increased when exenatide or liraglutide is taken in combination with insulin or sulfonylurea drugs; in the absence of other diabetes drugs that cause low blood glucose, hypoglycemia associated with GLP-1 agonist treatment is rare. The GLP-1 receptor agonists may decrease absorption of orally-administered drugs and this may be a critical issue in medications with a narrow therapeutic window or which require rapid absorption from the GI tract. The GLP-1 receptor agonists have a boxed warning regarding dose and duration dependent thyroid C-cell tumors occurring in animal studies with the incretin mimetics. A new alert from

The Food and Drug Administration (FDA) warns about findings suggesting an association between GLP-1 agonist treatment with pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis.¹⁻⁵ See Table 5 for a more comprehensive list of the warnings and precautions associated with the GLP-1 receptor agonists.

Table 5. Safety of the Glucagon-like Peptide-1 (GLP-1) Receptor Agonists¹⁻⁵

	Exenatide	Liraglutide
Boxed Warning	Dose- and duration-dependent thyroid C-cell tumors have developed in animal studies with exenatide extended release therapy; relevance in humans unknown.	Dose- and duration-dependent thyroid C-cell tumors have developed in animal studies with exenatide extended release therapy; relevance in humans unknown.
Special Alert	The Food and Drug Administration (FDA) is evaluating unpublished new findings that suggest an increased risk of pancreatitis and pancreatic duct metaplasia in patients with type 2 diabetes treated with incretin mimetics.	The Food and Drug Administration (FDA) is evaluating unpublished new findings that suggest an increased risk of pancreatitis and pancreatic duct metaplasia in patients with type 2 diabetes treated with incretin mimetics.
Contraindications	<u>Bydureon</u> TM : History of or family history of medullary thyroid carcinoma (MTC); patients with multiple endocrine neoplasia syndrome type 2 (MEN2)	History of or family history of medullary thyroid carcinoma (MTC); patients with multiple endocrine neoplasia syndrome type 2 (MEN2)
Warnings/Precautions	-Use may be associated with the development of anti-exenatide antibodies; high titers (6-12%) may result in an attenuation of response -Not recommended to be used in patients with gastroparesis or severe gastrointestinal disease -Not recommended in severe renal impairment (Clcr <30 mL/minute) or end-stage renal disease (ESRD); patients with ESRD may be more susceptible to GI effects -Pregnancy Risk Factor: C	-Serious hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported with use -Acute renal failure and chronic renal failure exacerbation have been reported -Pregnancy Risk Factor: C
Drug-Drug Interactions	-May reduce the rate and extent of absorption of orally-administered drugs; use with caution with drugs with a narrow therapeutic window or require rapid absorption from the GI tract -Concurrent use of insulin secretagogues may increase the risk of hypoglycemia -May decrease the serum concentration of contraceptives	-May reduce the rate and extent of absorption of orally-administered drugs; use with caution with drugs with a narrow therapeutic window or require rapid absorption from the GI tract -Concurrent use of insulin or insulin secretagogues may increase the risk of hypoglycemia
Adverse Reactions	Hypoglycemia (2-36%) Nausea (8-44%) Vomiting (4-13%) Diarrhea (2-20%) Constipation (6-10%) Injection site reaction (2-77%) Anti-exenatide antibodies (6-12%) Nervousness (9%) Dizziness (2-9%) Headache (5-9%) Fatigue (3-6%) Hyperhidrosis (3%) GERD (3-7%) Viral gastroenteritis (6-9%) Weakness (4%)	Nausea (28%) Diarrhea (17%) Vomiting (11%) Constipation (10%) Headache (9%) Hyperbilirubinemia (4%) Injection site reactions (2%) Anti-liraglutide antibodies (9%)

Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. NR = not reported.

Summary

Diabetes mellitus (DM) is a broad term describing metabolic disorders associated with hyperglycemia. Treatment of DM varies depending on the clinical subset of DM present and individual patient characteristics and may include a combination of antidiabetes agents in addition to therapies to treat other comorbid conditions associated with DM. The American Diabetes Association Standards of Medical Care in Diabetes (2013) recommends metformin as the preferred first-line agent for treatment of type 2 diabetes. A GLP-1 receptor agonist may be added to a patient's regimen if metformin monotherapy is contraindicated, not tolerated or does not achieve the target A1C at 3-6 months. Three Glucagon-like Peptide-1 (GLP-1) Receptor Agonists are currently available for use in the United States: exenatide twice daily (Byetta®), exenatide once weekly (Bydureon®) and liraglutide once daily (Victoza®).

The efficacy of GLP-1 receptor agonists was directly compared in one meta-analysis and four clinical trials. The evidence suggests both exenatide and liraglutide are efficacious in reducing A1C in patients with type 2 DM. Liraglutide therapy may be more efficacious in reducing A1C, fasting blood glucose, and weight than exenatide therapy. Exenatide therapy may be more efficacious in reducing post-prandial blood glucose levels than liraglutide therapy. No differences in efficacy were found in Asian patients or in patients of older age. The most common drug-related adverse reactions associated with the GLP-1 receptor agonists are gastrointestinal disturbances which appear to be dose-dependent and decrease over time. In clinical trials, higher rates of gastrointestinal adverse events were reported with liraglutide treatment while higher rates of injection site reactions were reported with exenatide once weekly treatment. Overall ranges of A1C reduction seen with exenatide, exenatide ER, and liraglutide in current literature are similar and choice of antidiabetes therapy should be based on individual patient characteristics, including: efficacy, cost, potential adverse effects, comorbidities, risk of hypoglycemia, and patient preference.

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Evidence Table. Meta-Analyses and Clinical Trials Evaluating the Glucagon-like Peptide-1 (GLP-1) Receptor Agonists³⁵⁻³⁹

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects
				Results	Change from baseline	
Meta-analyses						
Scott et al, 2013 ³⁸ Meta-analysis of 22 randomized, controlled trials	11,049	Patients with type 2 diabetes where mean change in HbA1c from baseline was reported	Exenatide 10 µg twice daily (BID) Exenatide 2 mg once weekly (QW) Insulin glargine Liraglutide once daily (1.2 or 1.8 mg) Placebo or no treatment Duration: ≥ 24 weeks	Liraglutide 1.8 mg ≥ Exenatide QW ≥ Liraglutide 1.2 mg ≥ Exenatide QD	Change in A1C level <ul style="list-style-type: none"> • exenatide BID > placebo • liraglutide 1.2 mg > placebo • liraglutide 1.8 mg > placebo • exenatide QW > exenatide BID • liraglutide 1.8 mg > exenatide BID • liraglutide 1.8 mg ≥ exenatide QW • liraglutide 1.8 mg ≥ liraglutide 1.2 mg 	Not reported
Exenatide Studies						
Drucker et al, 2008 ³⁹ Randomised, open-label trial <i>Funded by Amylin Pharmaceuticals</i>	295	Patients ≥16 years of age, with type 2 diabetes treated for at least 2 months before screening who's weight did not vary more than 10% for 6 months before screening	Exenatide 5 µg twice a day x 4 weeks, then 10 µg twice a day* (n = 147) Exenatide extended release 2.0 mg once a week* (n = 148) Duration: 30-weeks *Patients underwent a 3-day lead-in with exenatide 5 µg twice a day	Exenatide extended release ≥ Exenatide	Reduction in A1C level from baseline <ul style="list-style-type: none"> • exenatide: 1.5 • exenatide ER: 1.9, p < 0.05 A1C level ≤ 7% <ul style="list-style-type: none"> • exenatide: 61% • exenatide ER: 77%, p < 0.0039 Bodyweight changes <ul style="list-style-type: none"> • exenatide: -3.6 kg • exenatide ER: -3.7 kg 	Nausea <ul style="list-style-type: none"> • exenatide: 50 (34.5%) • exenatide ER: 39 (26.4%) Vomiting <ul style="list-style-type: none"> • exenatide: 27 (18.6%) • exenatide ER: 16 (10.8%) Diarrhea <ul style="list-style-type: none"> • exenatide: 19 (13.1%) • exenatide ER: 20 (13.5%) Constipation <ul style="list-style-type: none"> • exenatide: 9 (6.2%) • exenatide ER: 16 (10.8%) Injection site reactions <ul style="list-style-type: none"> • exenatide: 2 (1.4%) • exenatide ER: 26 (17.6%) Adverse event discontinuation rate <ul style="list-style-type: none"> • exenatide: 7 (4.8%) • exenatide ER: 9 (6.1%)

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects
				Results	Change from baseline	
Blevins et al, 2011 ³⁵ Randomized, multicenter, open-label trial	252	Patients aged ≥ 18 years with type 2 diabetes, A1c of 7.1–11.0%, BMI of 25–45 kg/m ² , and treated with diet/exercise or stable treatment with metformin, sulfonylurea, thiazolidinedione, or a combination for ≥ 2 months	Exenatide 5 μ g twice a day x 4 weeks, then 10 μ g twice a day* (n = 123) Exenatide extended release 2.0 mg once a week* (n = 129) Duration: 24-weeks *No lead-in period	Exenatide extended release \geq Exenatide	Reduction in A1C level from baseline • exenatide: 0.9 • exenatide ER: 1.6, p < 0.05 Bodyweight changes • exenatide: -1.4 kg • exenatide ER: -2.3 kg	Nausea • exenatide: 43 (35%) • exenatide ER: 18 (14%) Vomiting • exenatide: 11 (8.9%) • exenatide ER: 6 (4.7%) Diarrhea • exenatide: 5 (4.1%) • exenatide ER: 12 (9.3%) Injection site reactions • exenatide: 10% • exenatide ER: 13% Adverse event discontinuation rate • exenatide: 5% • exenatide ER: 5%
Exenatide vs. Liraglutide Studies						
Buse et al, 2009 ³⁷ Randomized, multicenter, open-label trial <i>Funded by Novo Nordisk</i>	464	Patients aged 18–80 years with type 2 diabetes, an A1c value of 7–11%, a BMI of ≤ 45 kg/m ² and stable treatment with metformin, sulphonylurea, or both, for ≥ 3 months	Exenatide 10 mcg subcutaneous twice a day with a 4-week dose-escalation period (n = 231) Liraglutide 1.8 mg subcutaneous once a day with a 2-week dose-escalation period (n = 233) Duration: 26-weeks	Liraglutide \geq Exenatide	Mean change in A1C from baseline • exenatide: -0.79% • liraglutide: -1.12%, p < 0.05 A1C level $\leq 7\%$ • exenatide: 43% • liraglutide: 54%, p = 0.0015 Bodyweight changes • exenatide: 2.87 kg • liraglutide: 3.24 kg	Serious adverse events • exenatide: 6 (2.6%) • liraglutide: 12 (5.1%) Constipation • exenatide: 6 (2.6%) • liraglutide: 12 (5.1%) Diarrhea • exenatide: 28 (12.1%) • liraglutide: 29 (12.3%) Nausea • exenatide: 65 (28%) • liraglutide: 60 (25.5%) Vomiting • exenatide: 23 (9.9%) • liraglutide: 14 (6%)

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes at End of Study Period		Adverse Effects
				Results	Change from baseline	
Buse et al, 2013 ³⁶ Randomized, multicenter, open-label trial <i>Funded by Amylin Pharmaceuticals</i>	912	Patients aged ≥ 18 years with type 2 diabetes with suboptimum glycaemic control despite lifestyle modification and maximum dose of oral anti-hyperglycemic drugs	Exenatide extended release 2.0 mg once a week (n = 461) Liraglutide 1.8 mg subcutaneous once a day with a 3-week dose-escalation period (n = 450) Duration: 26-weeks	Liraglutide \geq Exenatide	Mean change in A1C from baseline <ul style="list-style-type: none"> • exenatide: -1.28% • liraglutide: -1.48% Bodyweight changes (mean) <ul style="list-style-type: none"> • exenatide: 2.68 kg • liraglutide: 3.57 kg 	Serious adverse events <ul style="list-style-type: none"> • exenatide: 13 (3%) • liraglutide: 7 (2%) Constipation <ul style="list-style-type: none"> • exenatide: 6 (2.6%) • liraglutide: 12 (5.1%) Diarrhea <ul style="list-style-type: none"> • exenatide: 28 (6%) • liraglutide: 59 (13%) Nausea <ul style="list-style-type: none"> • exenatide: 43 (9%) • liraglutide: 93 (21%) Vomiting <ul style="list-style-type: none"> • exenatide: 17 (4%) • liraglutide: 48 (11%) Injection site reactions <ul style="list-style-type: none"> • exenatide: 48 (10%) • liraglutide: 5 (1%)