

Therapeutic Class Overview

Incretin Mimetics & Amylinomimetics

INTRODUCTION

- Diabetes mellitus affects approximately 29.1 million people in the United States (U.S.), which is approximately 9.3% of the population (American Diabetes Association [ADA] Diabetes Basics, 2016).
- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin (ADA Diabetes Basics, 2016).
- The classification of diabetes includes 4 clinical classes: 1) type 1 diabetes mellitus (T1DM) which results from beta-cell (β -cell) destruction, usually leading to absolute insulin deficiency, 2) type 2 diabetes mellitus (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance, 3) other specific types of diabetes due to other causes, eg, genetic defects in β -cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS] or after organ transplantation), and 4) gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (ADA, 2016).
- Insulin is the standard treatment for T1DM. Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The GLP-1 receptor agonists (albiglutide, dulaglutide, exenatide, exenatide extended-release [ER], liraglutide, and lixisenatide) were developed to mimic the effects of endogenous GLP-1 and are Food and Drug Administration (FDA)-approved as adjunctive therapy to diet and exercise to improve glycemic control in adults with T2DM.
- Pramlintide is the only amylin analog, or amylinomimetic, in the class, and is FDA-approved as an adjunctive treatment with insulin in patients with T1DM or T2DM who have failed to achieve desired glucose control despite optimal insulin therapy. It is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic β -cells that contributes to glucose control during the post-prandial period.
- This review will focus on the GLP-1 receptor agonists and pramlintide and their respective FDA-approved indications for treatment of diabetes. Liraglutide (SAXENDA[®]) is also indicated as adjunctive therapy for chronic weight management; however, the use of liraglutide for this indication will not be included in this review.
- Medispan class: Endocrine and Metabolic Drugs

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ADLYXIN [™] (lixisenatide)	Sanofi-Aventis	07/27/2016	-
BYETTA [®] (exenatide)	AstraZeneca	04/28/2005	-
BYDUREON [®] (exenatide ER)	AstraZeneca	01/27/2012	-
SYMLIN [®] (pramlintide)	AstraZeneca	03/16/2005	-
TANZEUM [®] (albiglutide)	GlaxoSmithKline	04/15/2014	-
TRULICITY [®] (dulaglutide)	Eli Lilly	09/18/2014	-
VICTOZA [®] (liraglutide)	Novo Nordisk	01/25/2010	-

(DRUGS@FDA, 2016)

INDICATIONS
Table 2. Food and Drug Administration Approved Indications

Indication	ADLYXIN (lixisenatide)	BYETTA (exenatide)	BYDUREON (exenatide ER)	SYMLIN (pramlintide)	TANZEUM (albiglutide)	TRULICITY (dulaglutide)	VICTOZA (liraglutide)
T1DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.				✓			
T2DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.				✓			
Adjunct to diet and exercise to improve glycemic control in adults with T2DM.	✓	✓	✓		✓	✓	✓
Limitations of Use							
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe only to patients for whom the potential benefits are considered to outweigh the potential risk.			✓		✓	✓	✓
Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in these patients.	✓	✓	✓		✓	✓	✓
Not indicated in treatment of patients with T1DM or for treatment of patients with diabetic ketoacidosis. Not a substitute for insulin in these patients.	✓	✓	✓		✓	✓	✓
Has not been studied in patients with severe gastrointestinal (GI) disease, including severe gastroparesis. Not recommended in patients with pre-existing severe GI disease.					✓	✓	
Has not been studied in patients with gastroparesis. Not recommended in patients with gastroparesis.	✓						
Not studied in combination with prandial/short-acting insulin.	✓	✓			✓		✓
Use with insulin has not been studied and is not recommended.			✓				
Use with basal insulin has not been studied.						✓	

(Prescribing information: BYETTA, 2015; BYDUREON, 2015; SYMLIN, 2015; VICTOZA, 2016; TANZEUM, 2016)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Albiglutide

- The approval of albiglutide was based on 8 pivotal trials involving over 5000 patients as a part of the HARMONY phase 3 program (TANZEUM FDA Medical Review, 2014; TANZEUM prescribing information, 2016). The majority of the trials were multicenter (MC), randomized, double-blind (DB), placebo-controlled (PC) or active control (AC) studies in adult patients with inadequately controlled T2DM (HbA1c 7% to 10%); however, 3 trials were open-label (OL). The primary outcome in each trial was the change in HbA1c from baseline at 26 to 104 weeks.
- HARMONY 1 demonstrated that albiglutide 30 mg once weekly was superior to placebo in patients taking concurrent pioglitazone with or without metformin at 52 weeks, with a mean reduction in HbA1c of 0.8% (Reusch et al, 2014).
- HARMONY 2 compared both albiglutide 30 mg and 50 mg once weekly to placebo in patients treated with diet and exercise alone and found that both were superior to placebo at 52 weeks. The least squares mean difference from placebo in HbA1c was -0.84% with the 30 mg dose and -1.04% with the 50 mg dose (Nauck et al, 2016).
- HARMONY 3 demonstrated that albiglutide 30 mg to 50 mg once weekly was superior to placebo, sitagliptin 100 mg once daily, and glimepiride 2 to 4 mg daily in patients taking concurrent metformin at 2 years, with a mean reduction in HbA1c of 0.6% (Ahren et al, 2014).
- HARMONY 4 was an OL trial comparing albiglutide (30 mg to 50 mg once weekly) to protocol titrated insulin glargine in patients taking concurrent metformin with or without an SFU. In this study, albiglutide demonstrated noninferiority to insulin glargine in HbA1c improvement at 52 weeks (Weissman et al, 2014).
- HARMONY 5 compared albiglutide (30 mg to 50 mg once weekly) to placebo and pioglitazone (30 mg to 45 mg per day) in patients taking concurrent metformin and glimepiride. At week 52, albiglutide did not meet the pre-specified noninferiority margin compared to pioglitazone; however, it was superior to placebo and had a mean reduction in HbA1c of 0.6% (Home et al, 2015).
- HARMONY 6, another OL trial, demonstrated that albiglutide 30 mg to 50 mg once weekly was noninferior to insulin lispro 3 times daily in patients taking concurrent pioglitazone with or without metformin at 26 weeks, with a mean reduction in HbA1c of 0.8% (Rosenstock et al, 2014a).
- HARMONY 7 was an OL study comparing albiglutide 50 mg once weekly to liraglutide 1.8 mg daily in patients taking concomitant metformin, TZD, SFU, or a combination of the medications. At week 32, the mean model adjusted change in HbA1c was -0.78% with albiglutide and -0.99% with liraglutide. Albiglutide failed to meet noninferiority ($P=0.085$) (Pratley et al, 2014).
- HARMONY 8 demonstrated that albiglutide 30 mg to 50 mg was superior to sitagliptin 25 to 100 mg in patients with impaired renal function on concurrent agents or lifestyle treatment at 26 weeks, with a mean reduction in HbA1c of 0.8% compared to a reduction of 0.5% with sitagliptin (Leiter et al, 2014).

Dulaglutide

- The approval of dulaglutide was based on 6 pivotal trials enrolling over 3,000 patients as a part of the AWARD phase 3 program. Trials evaluated the use of dulaglutide 0.75 mg and 1.5 mg strengths. The primary outcome in each trial was the change in HbA1c from baseline to 26 through 52 weeks.
- AWARD-1 demonstrated that once weekly dulaglutide resulted in significantly larger improvements in HbA1c at 26 weeks compared to placebo and exenatide in patients taking maximally tolerated doses of metformin and pioglitazone (Wysham et al, 2014).
- AWARD-2 was an OL study that demonstrated superiority of dulaglutide 1.5 mg once weekly and noninferiority of dulaglutide 0.75 mg once weekly compared to daily insulin glargine in terms of HbA1c reduction from baseline to week 52 (Giorgino et al, 2015).
- AWARD-3 was a DB study that demonstrated superiority of dulaglutide 0.75 mg and 1.5 mg once weekly to metformin in patients inadequately treated with diet and exercise with or without submaximal dosing of at least 1 oral antidiabetic drug (OAD). At 26 weeks, changes from baseline HbA1c were 0.78%, 0.71%, and 0.56% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin, respectively (Umpierrez et al, 2014).
- AWARD-4 was an OL, 52-week, noninferiority study which found that dulaglutide once-weekly (both 1.5 mg and 0.75 mg strengths) in combination with insulin lispro resulted in significantly greater improvement in glycemic control than insulin glargine in combination with insulin lispro ($P=0.005$ and $P=0.015$ for dulaglutide 1.5 mg and 0.75 mg, respectively) (Blonde et al, 2015).
- AWARD-5 was a DB trial that compared placebo, once-weekly dulaglutide (0.75 mg and 1.5 mg), and sitagliptin 100 mg once daily in uncontrolled metformin-treated patients. At weeks 52 and 104, both dulaglutide strengths were superior to sitagliptin in terms of HbA1c reduction from baseline ($P<0.001$ for all comparisons) (Nauck et al, 2014; Weinstock et al, 2015).

- AWARD-6 was an OL trial which demonstrated that, in patients taking concurrent metformin, dulaglutide 1.5 mg once weekly was noninferior to liraglutide once daily in HbA1c reduction from baseline to week 26 (Dungan et al, 2014).

Exenatide

- The efficacy of exenatide as add-on therapy to metformin alone, an SFU alone, or metformin in combination with an SFU was evaluated in 3 PC, 30-week, randomized controlled trials (RCTs). In all trials, there were significant decreases in HbA1c with exenatide compared to placebo ($P<0.001$, $P<0.002$, and $P<0.0001$, respectively) (Buse et al, 2004; DeFronzo et al, 2005; Kendall et al, 2005). Extensions of these 30-week trials demonstrated that the benefits of exenatide are sustained (Blonde et al, 2006; Buse et al, 2007; Klonoff et al, 2008; Ratner et al, 2006; Riddle et al, 2006).
- A trial evaluating exenatide as add-on therapy in patients currently taking a TZD found that at week 16, exenatide significantly decreased HbA1c ($P<0.001$), fasting plasma glucose (FPG) ($P<0.001$), and body weight ($P<0.001$) compared to placebo (Zinman et al, 2007).
- When exenatide was compared to glyburide as add-on therapy to metformin, exenatide significantly decreased body weight and body mass index (BMI) ($P<0.001$ for both), whereas the SFU caused significant increases in both ($P<0.05$ for both). Both treatments significantly decreased HbA1c, FPG, and postprandial plasma glucose (PPG) (exenatide; $P<0.001$ for all; glyburide; $P<0.001$ for all). Only exenatide significantly improved insulin resistance ($P<0.01$) and β -cell function ($P<0.05$) (Derosa et al, 2010).
- The EUREXA study compared the efficacy of exenatide and glimepiride as add-on therapy to metformin. Patients receiving exenatide exhibited greater reductions in HbA1c from baseline (-0.36%), compared to those receiving glimepiride (-0.21%; $P=0.002$) (Gallwitz et al, 2012).
- Several trials have compared exenatide to insulin therapy as add-on therapy to metformin and/or an SFU (Bunck et al, 2009; Bunck et al, 2010; Davies et al, 2009; Heine et al, 2005; Nauck et al, 2007; Secnik et al, 2006). Similar improvements in HbA1c between treatments were observed in 3 of the trials while mixed results were observed for decreases in FPG. Specifically, in 2 trials, insulin therapy was “superior” in decreasing FPG (P value not reported and $P<0.0001$), while in another trial there was no difference between the 2 treatments ($P=0.689$). Insulin therapy was associated with an increase in body weight compared to a decrease with exenatide (Bunck et al, 2009; Heine et al, 2005; Nauck et al, 2007). Patient-reported health outcome measures demonstrated no differences between exenatide or insulin therapy; both achieved significant improvements from baseline. However, neither treatment improved Diabetes Treatment Flexibility Scores ($P=0.93$ for both) (Secnik et al, 2006).
- Exenatide once weekly was also compared to daily insulin glargine in diabetic patients inadequately controlled with OADs. Following 26 weeks of therapy, exenatide was found to be statistically noninferior to insulin glargine for the change in HbA1c from baseline to endpoint (Inagaki et al, 2012).

Exenatide ER

- Approval of exenatide ER in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in 4 of the 5 trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy (Bergental et al, 2010; Blevins et al, 2011; Diamant et al, 2010; Drucker et al, 2008; Russell-Jones et al, 2012). Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA1c compared to exenatide ($P<0.005$), sitagliptin ($P<0.0001$), pioglitazone ($P=0.0165$), and insulin therapy ($P=0.017$), with no increased risk of hypoglycemia. In terms of decreases in body weight, exenatide ER was “superior” compared to sitagliptin ($P=0.0002$) and pioglitazone ($P<0.0001$), and similar compared to exenatide ($P=0.89$) (Bergental et al, 2010; Blevins et al, 2011; Drucker et al, 2008). As expected, GI-related adverse events (AEs) were reported more commonly with the incretin-based therapies. When compared to exenatide, exenatide ER was associated with lower incidences of nausea (14.0% vs. 35.0%) and vomiting (4.7% vs. 8.9%), and higher incidences of diarrhea (9.3% vs. 4.1%) and injection site-related AEs (13% vs. 10%) (Blevins et al, 2011).
- In the DURATION-4 trial, the decrease in HbA1c achieved with exenatide ER monotherapy was “superior” compared to sitagliptin ($P<0.001$) and similar compared to metformin ($P=0.62$) and pioglitazone ($P=0.328$). Exenatide ER and metformin were similar in terms of associated decreases in body weight, with exenatide ER achieving “superiority” compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more GI-related AEs, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin (Diamant et al, 2010).
- In a post-hoc analysis of 4 clinical trials, patients were treated with weekly exenatide for 52 weeks. Patients had significant lowering of HbA1c, blood pressure and low density lipoprotein (LDL) levels without an increase in weight or hypoglycemia (Bergental et al, 2013).

- The DURATION-6 trial compared HbA1c reductions between liraglutide once daily and exenatide once weekly in patients with T2DM previously treated with lifestyle modifications and oral agents. Both therapies resulted in improvements in glycemic control; however, greater reductions were noted with liraglutide (Buse et al, 2013).

Liraglutide

- Approval of liraglutide in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to an SFU (LEAD-1), metformin (LEAD-2), metformin plus a TZD (LEAD-4), metformin plus an SFU (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).
- In LEAD-1, liraglutide was compared to placebo or rosiglitazone as add-on therapy to an SFU. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg per day) significantly decreased HbA1c compared to placebo ($P<0.0001$ for all), with only higher doses achieving “superiority” compared to rosiglitazone ($P<0.001$ for both) (Marre et al, 2009).
- In LEAD-2, liraglutide was compared to placebo and an SFU as add-on therapy to metformin. Liraglutide significantly decreased HbA1c compared to placebo; however, similar decreases were observed with liraglutide compared to the SFU. Liraglutide was associated with significant decreases in body weight compared to placebo ($P<0.01$) and the SFU ($P<0.001$) (Nauck et al, 2009). Results of an 18-month OL extension trial were consistent with the DB study (Nauck et al, 2013).
- In LEAD-3, liraglutide was compared to an SFU as monotherapy, and liraglutide was “superior” in decreasing HbA1c ($P=0.0014$ and $P<0.0001$ for liraglutide 1.2 mg and 1.8 mg, respectively). In addition, increases in body weight were reported with the SFU, while liraglutide significantly decreased body weight ($P=0.027$) (Garber et al, 2009). In a 1-year extension trial, patients continuing liraglutide for a total of 2 years maintained significant improvements in HbA1c compared to the SFU (Garber et al, 2011).
- In LEAD-4 and LEAD-5, liraglutide was compared to placebo as add-on therapy to metformin plus an SFU and to a TZD. LEAD-5 also had an OL arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA1c, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials (Russell-Jones et al, 2009; Zinman et al, 2009). When compared to insulin therapy, decreases in HbA1c ($P=0.0015$) and body weight ($P<0.001$) and improvements in β -cell function ($P=0.0019$) were significantly greater with liraglutide. It was noted that decreases in PPG were not different between the 2 treatments, and the likelihood of patients achieving FPG goals were also similar (Russell-Jones et al, 2009).
- LEAD-6 was a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA1c compared to exenatide (1.12% vs 0.79%; $P<0.0001$), and a significantly greater proportion of patients receiving liraglutide achieved HbA1c goals of $<7\%$. Significant decreases in FPG were also achieved with liraglutide ($P<0.0001$); however, exenatide significantly decreased PPG after breakfast and dinner ($P<0.0001$ and $P=0.0005$) (Buse et al, 2009). A 14-week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits (Buse et al, 2010).

Lixisenatide

- Lixisenatide 20 mcg once daily was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin (with or without OADs). Its efficacy was compared with placebo, exenatide, and insulin glulisine. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the lixisenatide and comparator groups, was assessed at varying time points ranging between 12 and 26 weeks.
- GetGoal-Mono found that lixisenatide 20 mcg once daily as monotherapy resulted in significantly larger improvements in HbA1c at 12 weeks compared to placebo in patients with T2DM inadequately controlled on diet and exercise ($P<0.0001$) (Fonseca et al, 2012).
- GetGoal-F1 was a DB study which found that lixisenatide 20 mcg once daily as add-on therapy to metformin was superior vs. placebo in terms of HbA1c reduction from baseline to week 24. The least squares mean change from baseline was -0.26% for the placebo group vs. -0.72% for the lixisenatide group. The difference vs. placebo was -0.46% ($P<0.0001$) (Adlyxin prescribing information, 2016; Bolli et al, 2014).
- GetGoal-M-Asia demonstrated superiority of lixisenatide 20 mcg once daily as add-on therapy to metformin with or without an SFU compared to placebo in terms of HbA1c reduction from baseline to week 24 (Yu et al, 2014).
- GetGoal-S was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with an SFU with or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.58% ($P<0.0001$) (Adlyxin prescribing information, 2016; Rosenstock et al, 2014b).

- GetGoal-P was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with pioglitazone or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.48% (P<0.0001) (Adlyxin prescribing information, 2016; Pinget et al, 2013).
- In GetGoal-Duo 1, lixisenatide was compared to placebo as add-on therapy to basal insulin and metformin with or without a TZD. Treatment with lixisenatide resulted in a significant reduction in HbA1c at week 24 vs. placebo (Riddle et al, 2013a).
- In GetGoal-L, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without metformin while in Get-Goal-L-Asia, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without an SFU. Both studies found that lixisenatide was superior to placebo in terms of HbA1c reduction from baseline to week 24 (Riddle et al, 2013b; Seino et al, 2012).
- GetGoal-Duo 2 was a 26-week, OL trial that compared lixisenatide to insulin glulisine once daily or 3 times daily for intensification of optimized insulin glargine ± metformin in patients with T2DM uncontrolled on basal insulin ± OADs (ie, an SFU and/or a DPP-4 inhibitor, and/or a glinide). Lixisenatide was found to be noninferior to both insulin glulisine regimens in terms of HbA1c reduction from baseline to week 26. However, lixisenatide provided less HbA1c reduction than insulin glulisine 3 times daily and the difference was statistically significant; the least squares mean difference of lixisenatide vs. insulin glulisine 3 times daily was 0.23 (P=0.0002) (Adlyxin prescribing information, 2016; Rosenstock et al, 2016).
- GetGoal-X was a 24-week, OL trial that evaluated lixisenatide vs. exenatide twice daily as add-on therapy to metformin. Lixisenatide met the pre-specified noninferiority margin vs. exenatide twice daily for the difference in HbA1c reduction from baseline to week 24. However, lixisenatide provided less HbA1c reduction than exenatide and the difference was statistically significant; the least squares mean difference vs. exenatide was 0.17% (P=0.0175) (Adlyxin prescribing information, 2016; Rosenstock et al, 2013).

Cardiovascular (CV) outcomes

- Several RCTs designed to assess the impact of incretin-based therapy on CV outcomes are in progress, including trials with exenatide (EXSCEL, results expected in 2018), albiglutide (results expected in 2019), and dulaglutide (REWIND, results expected in 2019) (ClinicalTrials.gov, 2016).
- A MC, DB, PC, RCT (LEADER trial; N = 9340) was conducted to evaluate the long-term effects of liraglutide vs. placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, non-fatal myocardial infarction [MI], or non-fatal stroke) occurred in fewer patients in the liraglutide group (13.0%) vs. the placebo group (14.9%) (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from CV causes in the liraglutide group (4.7%) vs. the placebo group (6.0%) (HR, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (8.2%) vs. the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group (Marso et al, 2016a).
- A MC, DB, PC, RCT (ELIXA trial; N = 6068) evaluated the long-term effects of lixisenatide vs. placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome (ACS) event within 180 days of screening. The median follow-up was 25 months. It was found that the primary endpoint event (a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina) occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated noninferiority of lixisenatide to placebo (P<0.001), but did not demonstrate superiority (P=0.81). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (Pfeffer et al, 2015).
- Semaglutide, a once-weekly GLP-1 receptor agonist in the pipeline, demonstrated reduced CV risks in the SUSTAIN-6 trial when compared to placebo. A larger confirmatory trial is planned by Novo Nordisk, which is also expected to gather additional data on retinopathy complications reported in earlier studies (Marso et al 2016b, Skydsgaard 2016).

Meta-analyses

- Meta-analyses and Cochrane Reviews evaluating GLP-1 receptor agonists have found that they lead to decreases in HbA1c of ~1%, with greater decreases in body weight and systolic blood pressure compared to placebo and other antidiabetic agents (Wang et al, 2013; Shyangdan et al, 2011; Sun et al, 2015).
- Meta-analyses have revealed that incretin-based therapies are not associated with an increased risk of CV events (Monami et al, 2014b) or pancreatitis (Monami et al, 2014a) compared to placebo or other antidiabetic agents.

Pramlintide

- The safety and efficacy of pramlintide in patients with T1DM have been established in PC, RCTs when administered in addition to existing insulin regimens. In a 52-week, DB, MC, PC study, pramlintide significantly reduced HbA1c from

baseline compared to placebo (-0.39% vs -0.12%; P=0.0071) and was also associated with a significant weight loss compared to placebo (P<0.001) (Whitehouse et al, 2002). In a second 52-week study, patients experienced a significant reduction in HbA1c when receiving pramlintide 60 mcg 3 times daily (-0.41 vs. -0.18%; P=0.012) and pramlintide 60 mcg 4 times daily (-0.39 vs -0.18%; P=0.013) at 26 weeks. Treatment with pramlintide 3 or 4 times daily continued to maintain reductions in HbA1c at 52 weeks compared to treatment with placebo (P=0.011 and P=0.001 for the 3- and 4 times daily dosing, respectively) (Ratner et al, 2004).

- A meta-analysis of 3 studies assessing the effect of pramlintide as adjunctive therapy in patients with T1DM reported that, compared to placebo, pramlintide resulted in significant reductions in HbA1c and body weight from baseline to week 26 (0.3% and 1.8 kg, respectively; both P≤0.0009) (Ratner et al, 2005).
- A systematic review and meta-analysis of 8 PC, RCTs assessed the effect of pramlintide in patients with T2DM and in obese patients without diabetes. Four T2DM studies (N=930; 16 to 52 weeks duration) and 4 obesity studies (N=686; 6 to 24 weeks duration) were included. Of the T2DM studies, 3 studies used meal-time placebo as the comparator while 1 study used rapid-acting insulin as the comparator. When endpoint data from all T2DM studies were combined, pramlintide was associated with a small but significant reduction in HbA1c (mean difference: -0.33% [95% CI, -0.51 to -0.14]; P=0.0004). In the meta-analysis of the T2DM studies, patients on pramlintide were 1.52 times more likely to reach the HbA1c goal ≤7% than patients in the control group; however, this difference was not significant (P=0.18). Pramlintide was associated with a significant change in body weight in patients with T2DM compared to the control group (-2.57 kg [95% CI, -3.44 to -1.70]; P<0.00001) (Singh-Franco et al, 2011).

Clinical Guidelines

- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. Among T1DM patients, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management (ADA, 2016; Garber et al, 2016; Inzucchi et al, 2015).

SAFETY SUMMARY

- Contraindications:
 - Hypersensitivity to the drug or any of its components.
 - BYDUREON (exenatide ER), TANZEUM (albiglutide), TRULICITY (dulaglutide), and VICTOZA (liraglutide) are contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
 - SYMLIN (pramlintide): Gastroparesis and hypoglycemia unawareness.
- Boxed warnings:
 - BYDUREON (exenatide ER), TANZEUM (albiglutide), TRULICITY (dulaglutide) and VICTOZA (liraglutide)
 - Cause thyroid C-cell tumors in rats and mice. It is unknown if they cause thyroid C-cell tumors including MTC in humans.
 - They are contraindicated in patients with a personal or family history of MTC or in patients with MEN 2.
 - SYMLIN (pramlintide)
 - Use with insulin has been associated with an increased risk of severe hypoglycemia, particularly in patients with T1DM.
- Warnings/Precautions:
 - ADLYXIN (lixisenatide), BYETTA (exenatide), BYDUREON (exenatide ER), TANZEUM (albiglutide), TRULICITY (dulaglutide), and VICTOZA (liraglutide)
 - Pancreatitis – There have been reports of fatal and nonfatal hemorrhagic or necrotizing pancreatitis. Consider other therapies in patients with a history of pancreatitis.
 - Hypoglycemia – Risk is increased when used with insulin or insulin secretagogue.
 - Renal impairment – There have been post-marketing reports of altered renal function including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation.
 - BYETTA (exenatide), BYDUREON (exenatide ER), and TRULICITY (dulaglutide)
 - Severe GI disease – Use is not recommended.
 - ADLYXIN (lixisenatide), BYETTA (exenatide), and BYDUREON (exenatide ER)

- Immunogenicity – Patients can develop antibodies; glycemic control may be lost. Consider other therapies if there is worsening of glycemic control or failure to achieve the glycemic target.
- ADLYXIN (lixisenatide), BYETTA (exenatide), SYMLIN (pramlintide), and VICTOZA (liraglutide)
 - Pens should never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.
- SYMLIN (pramlintide)
 - Hypoglycemia – Risk is increased when used with insulin or insulin secretagogue.
- Adverse events:
 - The most common AEs seen with these agents are nausea and vomiting which generally decrease over time.
- Drug Interactions:
 - Orally administered drugs – Absorption of oral drugs can potentially be delayed. If absorption is critical to an oral drug's effectiveness, it should be given 1 hour before ADLYXIN (lixisenatide) or BYETTA (exenatide), and 1 hour before or 2 hours after SYMLIN (pramlintide).
 - Insulin – Mixing SYMLIN (pramlintide) and insulin can alter the pharmacokinetics of both products, leading to inadequate glucose control or hypoglycemia. They should never be mixed.
- Risk Evaluation and Mitigation Strategy (REMS) programs:
 - TANZEUM (albiglutide), TRULICITY (dulaglutide), and VICTOZA (liraglutide)
 - The REMS programs for these agents include a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC.
 - SYMLIN (pramlintide)
 - The REMS program includes a communication plan informing healthcare providers of the risk of severe hypoglycemia when this agent is used in combination with insulin as well as the importance of proper patient selection for treatment with this drug.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ADLYXIN (lixisenatide)	<u>Injection (50 mcg/mL):</u> 3 mL prefilled pen (14 pre-set doses; 10 mcg per dose) <u>Injection (100 mcg/mL):</u> 3 mL prefilled pen (14 pre-set doses; 20 mcg per dose)	Initiate at 10 mcg subcutaneously (SC) once daily for 14 days; on day 15, increase dosage to 20 mcg once daily	--	Inject in the abdomen, thigh, or upper arm. Administer within 1 hour before the first meal of the day, preferably the same meal each day.
BYETTA (exenatide)	<u>Injection (250 mcg/mL):</u> 1.2 mL prefilled pen, 5 mcg per dose, 60 doses 2.4 mL prefilled pen, 10 mcg per dose, 60 doses	Initiate at 5 mcg SC twice daily; increase to 10 mcg twice daily after 1 month based on clinical response.	--	Inject in the thigh, abdomen, or upper arm. Inject within 60 minutes prior to morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart).
BYDUREON (exenatide ER)	<u>Injection tray:</u> Single-dose vial containing 2 mg exenatide powder and 1 prefilled syringe delivering 0.65 mL diluent	Administer 2 mg SC once every 7 days (weekly).	If a dose is missed, administer as soon as noticed as long as the next dose is due at least 3 days	Inject in the thigh, abdomen, or upper arm. Administer at any time of day with or

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	<p><u>Pen injection:</u> Single-dose pen containing 2 mg exenatide per 0.65 mL diluent</p>		later.	<p>without meals.</p> <p>Administer immediately after the powder is suspended.</p>
SYMLIN (pramlintide)	<p><u>Injection (1,000 mcg/mL):</u> 1.5 mL disposable multidose SYMLINPen® 60 pen-injector for 15, 30, 45, and 60 mcg doses; 2.7 mL disposable multidose SYMLINPen 120 pen-injector for 60 and 120 mcg doses</p>	<p><u>T1DM</u> 15 mcg SC immediately prior to major meals. Increase the dose to the next increment (30 mcg, 45 mcg, or 60 mcg) when no clinically significant nausea has occurred for at least 3 days.</p> <p><u>T2DM</u> 60 mcg SC immediately prior to major meals. Increase dose to 120 mcg when no clinically significant nausea has occurred for 3 days.</p>	<p>Reduce preprandial, rapid-acting or short-acting insulin dosages, including fixed-mix insulins (70/30) by 50%. Adjust insulin doses to optimize glycemic control once the target dose of SYMLIN is achieved and nausea (if experienced) has subsided. Dose should be decreased if significant nausea persists.</p>	<p>Inject in the thigh or abdomen.</p> <p>Bring to room temperature prior to injecting.</p> <p>Administer immediately prior to each major meal (≥250 kcal or containing ≥30 g of carbohydrate).</p>
TANZEUM (albiglutide)	<p>Single-use pen for injection: 30 mg, 50 mg</p>	<p>30 mg SC once weekly; dose may be increased to 50 mg once weekly if the glycemic response is inadequate.</p>	<p>If a dose is missed, administer as soon as possible if within 3 days and resume dosing on usual day of administration. If it is more than 3 days after the missed dose, skip dose, and administer at next regularly scheduled weekly dose.</p>	<p>Inject in the thigh, abdomen, or upper arm.</p> <p>Administer on the same day each week. Day may be changed if necessary, so long as the previous dose was administered ≥4 days prior.</p> <p>Wait 15 minutes for the 30-mg pen and 30 minutes for the 50-mg pen after the lyophilized powder and diluent are mixed to ensure reconstitution.</p>
TRULICITY (dulaglutide)	<p>Single-dose pen or prefilled syringe: 0.75 mg/0.5 mL and 1.5 mg/0.5 mL</p>	<p>0.75 mg SC once weekly; dose can be increased to 1.5 mg once weekly for additional glycemic control.</p>	<p>If a missed dose occurs and there are at least 3 days (72 hours) until the next scheduled dose, administer the dose. If less</p>	<p>Inject in the thigh, abdomen, or upper arm.</p> <p>May be given any time of day, with or without food.</p>

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			than 3 days remain before the next scheduled dose, skip the missed dose and administer the next dose on the regularly scheduled day.	The day of weekly administration may be changed if necessary as long as the last dose was administered 3 or more days before.
VICTOZA (liraglutide)	Injection (6 mg/mL): 3 mL pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg	0.6 mg SC once daily for 1 week, then increase the dose to 1.2 mg once daily. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg once daily.	The initial dose is intended to reduce GI symptoms during initial titration, and is not effective for glycemic control.	Inject in the thigh, abdomen, or upper arm. Administer once daily at any time of day, independently of meals. If VICTOZA is stopped for more than 3 days, start at 0.6 mg per day again.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ADLYXIN (liraglutide)	No overall differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out.	Safety and efficacy have not been established.	No dose adjustment is recommended in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m ²) or moderate (eGFR 30 to 59 mL/min/1.73 m ²) renal impairment, but close monitoring for AEs and for changes in renal function is recommended. Clinical experience in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m ²) is extremely limited; patients should be closely monitored	No pharmacokinetic study has been performed in patients with acute or chronic hepatic impairment. Hepatic dysfunction is not expected to affect the pharmacokinetics of ADLYXIN.	There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			for GI AEs and for changes in renal function. There is no therapeutic experience in patients with end-stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m ²); it is not recommended to use ADLYXIN in this population.		
BYETTA (exenatide)	No differences in safety or efficacy were observed between elderly and younger patients; however, because elderly patients are more likely to have decreased renal function, caution is advised when initiating these drugs in the elderly.	Safety and efficacy have not been established.	BYETTA is not recommended for use in patients with ESRD or severe renal impairment (creatinine clearance [CrCL] <30 mL/min). Caution should be applied when initiating or escalating doses from 5 to 10 mcg in patients with moderate renal impairment (CrCL 30 to 50 mL/min).	Hepatic dysfunction is not expected to affect blood concentrations.	Pregnancy category C* There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.
BYDUREON (exenatide ER)	No differences in safety or efficacy were observed between elderly and younger patients; however, because elderly patients are more likely to have decreased renal function, caution is advised when initiating these drugs in the elderly.	Safety and efficacy have not been established.	BYDUREON is not recommended for use in patients with ESRD or severe renal impairment (CrCL <30 mL/min). Caution is advised in patients with renal transplantation or moderate renal impairment (CrCL 30 to 50 mL/min).	Hepatic dysfunction is not expected to affect blood concentrations.	Pregnancy category C* There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
SYMLIN (pramlintide)	No consistent differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out.	Safety and efficacy have not been established.	No dose adjustment is recommended.	Use has not been studied in patients with hepatic impairment.	Pregnancy category C* Unknown whether excreted in breast milk; use with caution.
TANZEUM (albiglutide)	No overall differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out.	Safety and efficacy have not been established.	No dose adjustment is required in mild, moderate, or severe renal impairment. Experience in patients with severe renal impairment is limited. In clinical trials, GI AEs increased as renal function decreased.	No clinical trials were conducted to examine the effects of mild, moderate, or severe hepatic impairment on the pharmacokinetics of TANZEUM. Therapeutic proteins such as TANZEUM are catabolized by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of TANZEUM.	Pregnancy category C* There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk. Consider stopping at least 1 month before a planned pregnancy due to the long washout period.
TRULICITY (dulaglutide)	No overall differences in safety or efficacy have been detected in patients 65 years of age and older. However, greater sensitivity of some older individuals cannot be ruled out.	Safety and efficacy have not been established.	There is limited clinical experience in patients with severe renal impairment or ESRD. TRULICITY should be used with caution, and if these patients experience GI AEs, renal function should be closely monitored.	There is limited clinical experience in patients with mild, moderate, or severe hepatic impairment. Therefore, this drug should be used with caution in these patient populations.	Pregnancy category C* There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					known whether these drugs are excreted in human milk.
VICTOZA (liraglutide)	No overall differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out.	Safety and efficacy have not been established.	No dose adjustment is recommended for patients with renal impairment. The safety and efficacy of VICTOZA was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m ²). There is limited experience with this drug in patients with severe renal impairment, including ESRD. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Caution should be used in patients who experience dehydration.	There is limited experience in patients with mild, moderate, or severe hepatic impairment. Therefore, caution is advised in this patient population. No dose adjustment is recommended for patients with hepatic impairment.	Pregnancy category C* There are no adequate and well-controlled studies in pregnant women. GLP-1 receptor agonists should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.

* Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- The GLP-1 receptor agonists, or incretin mimetics, exenatide (BYETTA), exenatide ER (BYDUREON), albiglutide (TANZEUM), dulaglutide (TRULICITY), liraglutide (VICTOZA), and lixisenatide (ADLYXIN) are incretin-based antidiabetic therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult patients with T2DM. Pramlintide (SYMLIN) is the only agent within the amylinomimetic medication class and is FDA-approved as adjunctive therapy in patients with T1DM or T2DM who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
- The incretin mimetics are available as SC injections to be administered in the abdomen, thigh, or upper arm. BYETTA is administered twice daily (60 minutes prior to meals); VICTOZA is administered once daily (independent of meals); and ADLYXIN is administered once daily (1 hour prior to the first meal of the day). BYDUREON, TANZEUM, and

TRULICITY are administered once weekly. SYMLIN is available as a SC injection to be administered immediately prior to each major meal. These agents are currently available as branded products only.

- The incretin mimetics have been studied extensively in combination with, and in comparison to, a variety of antidiabetic therapies. The agents are significantly more effective than placebo in reducing HbA1c, FPG, PPG, and body weight. Efficacy data comparing treatment to an SFU, TZD, DPP-4 inhibitor or insulin is mixed, with the GLP-1 agonists achieving significantly greater or comparable benefits in glycemic outcomes.
- Several CV outcomes trials evaluating GLP-1 receptor agonists in patients with T2DM and high CV risk have been published. The LEADER trial demonstrated reduced CV risk with liraglutide vs. placebo (Marso et al, 2016a), whereas the ELIXA trial did not demonstrate a statistically significant difference between lixisenatide vs. placebo (Pfeffer et al, 2015). Results of the SUSTAIN-6 trial for semaglutide, an agent which has not yet been FDA approved, have also been published (Marso et al, 2016b).
- Overall, the AE profiles of the GLP-1 receptor agonists are similar. With the exception of ADLYXIN and BYETTA, all of the agents have a boxed warning regarding the risk of thyroid C-cell tumors. Other warnings include increased risks of pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. TANZUEM, TRULICITY, and VICTOZA have REMS programs which include a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC.
- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. The incretin mimetics are recommended as a potential second-line treatment option to be added to metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. No one incretin mimetic is recommended or preferred over another. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. For T1DM, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management (ADA, 2016; Garber et al, 2016; Inzucchi et al, 2015).

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