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 2017*).
- 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 2017*).
- 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 2017*).
- 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.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adlyxin (lixisenatide)	-
Bydureon (exenatide ER)	-
Byetta (exenatide)	-
Symlin (pramlintide)	-
Tanzeum (albiglutide)	-
Trulicity (dulaglutide)	-
Victoza (liraglutide)	-

(*DRUGS@FDA 2017*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. FDA 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.			✔				

(Prescribing information: *Adlyxin 2016*, *Bydureon 2017*, *Byetta 2015, Symlin 2016, Victoza 2016, Tanzeum 2016, Trulicity 2017*)

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 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 (*Bergenstal 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 ($p = 0.89$) (*Bergenstal 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 (*Bergenstal 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

- The approval of lixisenatide was based on several phase 3 trials as part of the GetGoal clinical trial program. 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 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*).
- A meta-analysis of 76-week data from 5 trials in the GetGoal clinical trial program (GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-P, and GetGoal-L) supported the sustained efficacy and tolerability of lixisenatide (*Broglio et al 2017*).

Cardiovascular (CV) outcomes

- Several RCTs designed to assess the impact of incretin-based therapy on CV outcomes are in progress, including trials for albiglutide (results expected in 2018) and dulaglutide (REWIND, results expected in 2018) (*ClinicalTrials.gov 2017)*. The EXSCEL trial examining exenatide ER was completed in 2017; the manufacturer announced that the drug met its primary objective of non-inferiority vs. placebo for the major adverse CV events (MACE) endpoint. The results of the EXSCEL trial will be presented at the European Association for the Study of Diabetes (EASD) annual meeting in September 2017 (*Astra Zeneca Press Release 2017*).
- 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*).
  - In June 2017, the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the FDA completed its meeting regarding the sponsor's supplemental New Drug Application (sNDA) for inclusion of the LEADER trial data in the label for liraglutide. The Advisory Committee voted 19-0 in favor of liraglutide on the question: "Do the results of LEADER trial establish that the use of liraglutide in patients with T2DM is not associated with excess CV risk?" It voted 17-2 in favor of liraglutide on the question: "Does the LEADER trial provide substantial evidence needed to establish that liraglutide (1.8 mg) reduces CV risk in patients with T2DM?" Regulatory feedback is expected in Q3 2017 (*Novo Nordisk Press Release 2017*).
- 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*).
- A systematic review and mixed-treatment comparison analysis of GLP-1 receptor agonists found that there were no differences in efficacy within the short-acting (exenatide or lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide ER, liraglutide) groups. However, dulaglutide, liraglutide, and exenatide ER were superior to exenatide and lixisenatide at lowering HbA1c and FPG. There were no clinically meaningful differences between agents in weight loss or hypoglycemia. Albiglutide had the lowest risk of nausea and diarrhea, while exenatide ER had the lowest risk of vomiting (*Htike et al 2016*).
- Meta-analyses have revealed that incretin-based therapies are not associated with an increased risk of pancreatitis (*Monami et al 2017a*) and appear to reduce all-cause mortality, CV mortality, and the incidence of MI (*Monami et al 2017b*) 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 systematic review and meta-analysis of 10 randomized, PC studies (N = 3297) evaluating the effect of pramlintide as adjunctive therapy to insulin in patients with T1DM found that, compared to placebo, pramlintide resulted in significant reductions in HbA1c (p < 0.001), total daily insulin dose (p = 0.024), mean mealtime insulin dose (p < 0.001), body weight (p < 0.001), and PPG (p = 0.002) (*Qiao et al 2017*).
- 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 in the general treatment algorithm; however, the ADA guidelines state that liraglutide and the SGLT2 inhibitor, empagliflozin, should be considered in patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease, as they have been shown to reduce CV and all-cause mortality when added to standard care. 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 2017; Garber et al 2017, Inzucchi et al 2015*).

SAFETY SUMMARY

- GLP-1 receptor agonists are contraindicated in patients with hypersensitivity to any component of the products. With the exception of exenatide and lixisenatide, they are also contraindicated in those with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome, type 2 (MEN 2).
- All GLP-1 receptor agonists, except exenatide and lixisenatide, carry a boxed warning for risk of thyroid C-cell tumors. Other safety risks include pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, renal impairment, and lack of conclusive evidence for macrovascular risk reduction. Common AEs include: nausea, diarrhea, vomiting, headache, and injection site reactions.
- Pramlintide is contraindicated in patients with hypersensitivity to any component of the drug and in those with hypoglycemia unawareness and confirmed gastroparesis. It has a boxed warning for increased risk of hypoglycemia, particularly in patients with T1DM. Common AEs include nausea, headache, anorexia, and vomiting; the incidence of nausea tends to be higher at the beginning of treatment and decreases with time in most patients. Gradual titration of the dose minimizes the incidence and severity of nausea
- Albiglutide, exenatide, exenatide ER, liraglutide, and pramlintide are Pregnancy Category C. Dulaglutide and lixisenatide are uncategorized in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR).
  - There are no adequate and well-controlled studies in pregnant women. These drugs 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.
  - Due to the long washout period for albiglutide, discontinuation of the drug at least 1 month before a planned pregnancy should be considered.
- Albiglutide, dulaglutide, and liraglutide have a Risk Evaluation and Mitigation Strategy (REMS) program consisting of a communication plan to inform healthcare providers about the potential risk of MTC and acute pancreatitis (*REMS@FDA Web site 2017*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adlyxin (lixisenatide)	Injection	SC	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.
Bydureon (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the powder is suspended.
Byetta (exenatide)	Injection	SC	Twice daily	Inject in the thigh, abdomen, or upper arm. Inject within 60 minutes prior to the morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart).
Symlin (pramlintide)	Injection	SC	Prior to major meals	Inject in the thigh or abdomen. Administer immediately prior to each major meal. Reduce mealtime insulin doses by 50%. Adjust insulin doses to optimize glycemic control once the target dose of pramlintide is achieved and nausea (if experienced) has subsided. The dose should be decreased if significant nausea persists.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Tanzeum (albiglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. 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.
Trulicity (dulaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Victoza (liraglutide)	Injection	SC	Once daily	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.

CONCLUSION

- The GLP-1 receptor agonists exenatide, exenatide ER, albiglutide, dulaglutide, liraglutide, and lixisenatide are incretin-based antidiabetic therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult patients with T2DM. Pramlintide 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. Exenatide is administered twice daily (60 minutes prior to meals); liraglutide is administered once daily (independent of meals); and lixisenatide is administered once daily (1 hour prior to the first meal of the day). Exenatide ER, albiglutide, and dulaglutide are administered once weekly. Pramlintide is available as a SC injection to be administered immediately prior to each major meal.
- 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 lixisenatide and exenatide, 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. Albiglutide, dulaglutide, and liraglutide 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 in the general treatment algorithm; however, the ADA guidelines recommend that liraglutide and the SGLT2 inhibitor, empagliflozin, should be considered in patients with long-standing suboptimally controlled T2DM and established atherosclerotic CV disease, as they have been shown to reduce CV and all-cause mortality when added to standard care. 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 2017; Garber et al 2017, Inzucchi et al 2015*).

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