Background
Diabetes Mellitus (DM) remains the seventh leading cause of death in the United States in 2010, with 69,071 death listing diabetes as the underlying cause of death, and a total of 234,051 death certificates listing it as an underlying or contributing cause of death.\(^1\) Based on the Centers for Disease Control and Prevention 2014 National Diabetes Statistics Report, 29.1 million people (9.3\%) have been diagnosed with Diabetes of which only 21.0 million people have been diagnosed.\(^2\) In 2012 the total cost of being diagnosed with Diabetes in the United States was $245 billion; $176 billion for direct medical costs and $69 billion in reduced productivity.\(^3\) Currently, there are twelve drug classes for the treatment of DM with varying degrees of HbA1c reduction. Of the twelve drug classes for treatment, three of them require injections, in order of greatest to least reduction of HbA1c they are insulin (1.5-3.5 reduction in HgA1c), GLP-1 agonists (0.6-1.5), and amylin analogs (0.5-0.7). Of the injectable agents only GLP-1 agonists have an available formulation that can be administered once weekly. Currently, there are four FDA approved glucagon-like peptide-1 (GLP-1) agonists for the treatment of type 2 diabetes mellitus, they are Trulicity® (dulaglutide), Tanzeum® (albiglutide), Bydureon/Byetta® (exenatide), and Victoza® (liraglutide).

Pathophysiology
The human body regulates glucose using hormones called insulin and amylin (made from pancreatic β cells), glucagon (from pancreatic α cells), gastrointestinal peptides such as glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 is released when an individual consumes a meal; this then stimulates the production and secretion of insulin. However, the secretion of insulin is less when carbohydrates are given intravenously as opposed to orally; also known as the incretin effect. After GLP-1 is secreted, it binds to specific GLP-1 receptors found in pancreatic β-cells, pancreatic ducts, gastric mucosa, kidney, lung, heart, skin, immune cells, and the hypothalamus. GLP-1’s main effect is to stimulate a glucose-dependent insulin release from the pancreatic islets. In addition, it can also slow gastric emptying, inhibit inappropriate post-meal glucagon release, and reduce food intake via appetite centers in the brain. Moderate weight loss can be expected in patients because of slow gastric emptying and reduced food intake.\(^4\) Natural human GLP-1 is degraded by dipeptidyl peptidase 4 (DPP-4) very quickly and

Figure 1: GLP-1 Pathophysiology

http://www.globalpharmacstorenews.com/wp-content/uploads/2012/01/GLP-1.jpg

accounts for GLP-1’s half-life of one or two minutes.\(^5\)

DULAGLUTIDE ADVANTAGES\(^6,7\)
The GLP-1 agonists all have notable differences; dulaglutide is ready to use and does not need to be reconstituted like albiglutide or exenatide. The dulaglutide pen is also the only GLP-1 device that has a pre-attached, hidden needle.\(^8\) From the four GLP-1 medications exenatide and dulaglutide are the only ones that offer a once a week dosing but from these two, dulaglutide is the only one that is a ready to use pen device with an automatic injector.

PHARMACODYNAMICS
In adults with Diabetes Mellitus type 2, once weekly administration with dulaglutide resulted in a reduction of fasting blood sugar (FBS) of -25.6 mg/dL, 2-hour post-prandial glucose (PPG) concentrations of -59.5 mg/dL, and postprandial salivary glucose incremental AUC of -197 mg h/dL when compared to placebo. These effects were sustained after 6 weeks of dosing with the 1.5 mg dose.\(^9\) As for the glucose-dependent insu...
Dulaglutide, A New Glucagon-Like Peptide-1 Agonist for the Treatment of Type 2 DM (Continued)

lin secretion and reduction of glucagon secretion, dulaglutide 0.75 mg and 1.5 mg once weekly, increased fasting insulin from baseline to week 26 by 35.38 and 17.50 pmol/L, respectively. A reduction in fasting glucagon concentration was also seen (-1.71 with 0.75 mg dose)and (-2.05 pmol/L with 1.5 mg dose).

Pharmacokinetics
After subcutaneous administration, time to maximum plasma concentration of dulaglutide at steady-state was between 24 to 72 hours (median of 48 hours). Mean absolute bioavailability was 65% (0.75 mg dose) and 47% (1.5 mg dose). Distribution varied between 14.3 to 26.4 L (0.75 mg dose) and 9.3 to 33 L (1.5 mg dose). The elimination half-life of dulaglutide for both doses was approximately 5 days.

Dulaglutide as monotherapy
In a 52 week double blind study (26th week was the primary endpoint), 807 enrolled patients were either inadequately controlled with diet and exercise or had a diet and exercise plan with the addition of one anti-diabetic agent at submaximal dose. These patients were randomized to either receive dulaglutide 0.75 mg once weekly, dulaglutide 1.5 mg once weekly, or metformin 1500 to 2000 mg/day following a two week washout. Most patients previously treated with an antidiabetic agent received metformin (~90%) on average a 1000 mg daily dose and the remainder received a sulfonylurea (10%). Patients’ average age was 56 years and a mean duration of type 2 diabetes was 3 years. Forty-four percent were male; White (74%), Black (7%); and Asian (8%). Twenty-nine percent of the study popu-
Combination Therapy with dulaglutide

A 104 week placebo-controlled, double-blind study with 972 patients were randomized to placebo, dulaglutide 0.75 mg once weekly, dulaglutide 1.5 mg once weekly, or sitagliptin 100 mg/day (after 26 weeks, patients in the placebo treatment group received blinded sitagliptin 100 mg/day for the remainder of the study), all as add on to metformin. The primary endpoint was findings at week 52; randomization occurred the 11th week to allow for metformin to be titrated. Patients had a mean age of 54 years and mean duration of type 2 diabetes of 7 years. Participants were 47% male; race included white (52%), black (4%) and Asian (25%).

During the 26th week HbA1c reduction was 0.1% for placebo, 1.0% (dulaglutide 0.75 mg), 1.2% (dulaglutide 1.5 mg), and 0.6% (sitagliptin 100mg/day). The percentage of patients who achieved HbA1c <7.0% was 22% (placebo), 56% (dulaglutide 0.75 mg), 62% (dulaglutide 1.5 mg), and 39% (sitagliptin). Mean reduction in fasting glucose was 9 mg/dL (placebo), 35 mg/dL (dulaglutide 0.75 mg), 41 mg/dL (dulaglutide 1.5 mg), and 18 mg/dL (sitagliptin). Overall, participants on metformin plus dulaglutide 0.75 mg or 1.5 mg once weekly resulted in a statistically significant reduction in HbA1c compared to placebo (at 26 weeks) and sitagliptin.

Place in Therapy

Dulaglutide has been indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 Diabetes Mellitus. Dulaglutide is not recommended as the first-line medication to treat diabetes. It has not been studied in people who have had inflammation of the pancreas (pancreatitis). Dulaglutide should not be used if a history of severe gastrointestinal (GI) disease, type 1 diabetes, or a person with diabetic ketoacidosis exists. It is not a substitute for insulin but the reduction in fasting and postprandial glucose can be observed after a single dose. It has not been studied with long-acting insulin or in children under 18 years of age. If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a glucagon-like peptide 1 (GLP-1) receptor agonist, or insulin.

Dose & Administration

Each single-dose pen or prefilled syringe contains 0.5 mL of solution. Initial dose is 0.75 mg once weekly however, the dose may be increased to 1.5 mg once weekly for additional glycemic control. The maximum recommended dose is 1.5 mg once weekly. If a dose is missed it can be administered as soon as possible if they are within 3 days (72 hours) from thenext scheduled dose. If less than 3 days remain prior to the next scheduled dose, skip the missed dose and administer the next dose on the regularly scheduled day. No clinically relevant change in dulaglutide pharmacokinetics was observed in participants with renal impairment including end-stage renal disease (ESRD). It must be subcutaneously injected into the abdomen, thigh, or upper arm.

| Table 1: Adverse Reactions in Placebo-Controlled Trials Reported in 25% of TRULICITY-Treated Patients |
|-----------------------------------|------------------|------------------|------------------|
| Adverse Reaction                  | Placebo (%)      | Trulicity 0.75 mg (%) | Trulicity 1.5 mg (%) |
| Nausea                            | 1.6             | 1.8              | 2.1              |
| Diarrhea                          | 0.7             | 0.8              | 1.2              |
| Vomiting                          | 2.3             | 0.6              | 1.2              |
| Abdominal Pain                    | 4.8             | 0.5              | 9.4              |
| Decreased Appetite                | 1.6             | 4.2              | 0.8              |
| Dyspepsia                         | 2.3             | 4.1              | 5.8              |
| Fatigue                           | 2.8             | 4.2              | 5.0              |

ADR

The most common adverse reactions reported in ≥5% of patients taking dulaglutide are nausea, diarrhea, vomiting, abdominal pain, and decreased appetite.1 (Table 1)

Warning

Dulaglutide causes thyroid C-cell tumors in rats; however it is unknown whether dulaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. Dulaglutide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Drug-Drug interactions

Since dulaglutide slows gastric emptying, it may potentially reduce the rate of absorption of other oral medications. However, clinical pharmacology studies demonstrate that dulaglutide did not affect the absorption of orally administered medications to a clinically relevant degree.

REFERENCES


Continued on page 19
Dulaglutide, A New Glucagon-Like Peptide-1 Agonist for the Treatment of Type 2 DM
(Continued)

Figure 2: AACE Algorithm


Pedro Sanchez is a PharmD candidate with the UTEP/UT Austin Cooperative Pharmacy Program.

Margie Padilla, PharmD, CDE, BCACP is a Clinical Assistant Professor with the UTEP/UT Austin Cooperative Pharmacy Program.