Trulicity (Dulaglutide): A New GLP-1 Receptor Agonist Once-Weekly Subcutaneous Injection Approved for the Treatment of Patients with Type 2 Diabetes

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Diabetes, a chronic disease that is often accompanied by multiple comorbidities and health complications, is the seventh leading medical cause of death in the United States. In fact, the mortality rate for patients with diabetes is 1.5 times higher than for individuals without diabetes.[1] Diabetes affects an estimated 29.1 million individuals in the United States—an alarming 9.3% of the US population.[1] In addition, an estimated 37% of US adults aged ≥20 years have prediabetes, according to the 2009-2012 National Health and Nutrition Examination Survey data.[1] The prevalence of diabetes is projected to increase from 1 in 10 adults today to 1 in 3 adults by 2050, coinciding with the aging of the baby boom generation during the next few decades.[2] Type 2 diabetes mellitus accounts for approximately 90% to 95% of all cases of diabetes.

Diabetes is a major cause of heart disease and stroke. In addition, diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness in US adults.[1] Furthermore, patients with diabetes are at an increased risk for other complications, including nerve disease, nonalcoholic fatty liver disease, periodontal disease, erectile dysfunction, hearing loss, depression, and pregnancy complications.[1]

The total estimated cost for patients with diagnosed diabetes in 2012 totaled $245 billion, including $176 billion in direct medical costs and $69 billion in indirect costs (ie, increased absenteeism, reduced productivity, lost productivity as a result of early mortality, and the inability to work resulting from disability).[3] These 2012 costs represent a 41% increase from diabetes-related costs of $174 billion in 2007. Overall, the medical expenses for patients with diabetes are 2.3 times higher than for individuals without diabetes.[3]

According to the American Diabetes Association (ADA), diabetes management is complex, generally requiring multiple risk reduction strategies in addition to glycemic control.[4] Diabetes management demands an ongoing, patient-tailored approach that considers the whole patient—glycemic control to prevent or reduce microvascular complications, as well as strategies to address obesity and prediabetes as the underlying risk factors for diabetes and for related macrovascular complications. These approaches generally include dietary and other behavioral and lifestyle changes, which are important aspects of diabetes care.[4] Adequate glycemic control has been shown to reduce the morbidity and mortality of diabetes by decreasing chronic complications.[4] Lowering the hemoglobin (Hb) A_{1c} levels to 7% or below reduces microvascular complications, and, if reached soon after the diagnosis of diabetes, is associated with a long-term reduction in macrovascular disease.[4]

The ADA's 2013 position statement on the standards of care for diabetes recommends a target HbA_{1c} level of <7% for the majority of adult patients with diabetes.[4] The ADA acknowledges that the stringency of this goal may need to be modified based on the patient's duration of diabetes, comorbidities, age, known cardiovascular or advanced microvascular complications, and other patient-specific factors.[4] In a 2013 consensus statement, the American Association of Clinical Endocrinologists (AACE) recommended an HbA_{1c} target goal of <6.5% in the majority of patients with type 2 diabetes, with the caveat that this goal may be too aggressive for some patients and not aggressive enough for other patients (ie, younger patients for whom a lower target may prevent later complications).[5] The AACE also states that lifestyle modification and antihyperglycemic pharmacotherapy should aim to reach clinical and biochemical glucose targets, avoid hypoglycemia, assist with weight loss and minimize weight gain in obese individuals, and reduce or avoid increasing cardiovascular disease risk.[5]

Despite the progress made in the number of US adults who reach the target HbA_{1c} level of <7%, there is room for more improvement.[6] Ongoing clinical management, patient engagement, education, and the development of novel therapies may help to improve glycemic control and outcomes for patients with diabetes.[6]

The ADA recommends metformin as the initial therapy for type 2 diabetes; if another treatment or a com-

bination therapy is warranted, available agents include sulfonylureas, thiazolidinediones, dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists, insulin, and other agents.[7]

The development of the GLP-1 receptor agonist and the DPP-4 inhibitor classes, both of which target the incretin system, represents an important advancement in the management of type 2 diabetes.[8] The long-acting GLP-1 receptor agonists improve glycemic control and help to promote weight loss. Furthermore, based on their glucose-dependent mechanism of action, the GLP-1 receptor agonists have a low risk for hypoglycemia.[8]

Dulaglutide: A New Once-Weekly Option

On September 18, 2014, dulaglutide (Trulicity; Eli Lilly), a once-weekly subcutaneous injection, was approved by the US Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[9] Dulaglutide is a GLP-1 receptor agonist that was shown to reduce fasting and postprandial glucose after a single dose.[10]

Dulaglutide is not recommended as first-line therapy for patients whose diabetes is inadequately controlled with diet and exercise.[10] In addition, dulaglutide is not recommended in patients with type 1 diabetes, diabetic ketoacidosis, or a preexisting severe gastrointestinal disease. Du-

laglutide has not been studied in patients with a history of pancreatitis or in combination with basal insulin.[10]

According to Mary Parks, MD, Deputy Director, Office of Drug Evaluation II in the FDA Center for Drug Evaluation and Research, "Type 2 diabetes is a serious chronic condition that causes blood glucose levels to rise higher than normal. Trulicity is a new treatment option, which can be used alone or added to existing treatment regimens to control blood sugar levels in the overall management of type 2 diabetes."[9]

The FDA requires a Risk Evaluation and Mitigation Strategy program for dulaglutide to inform healthcare professionals about dulaglutide's serious associated risks.[9] The FDA also requires several postmarketing studies to be conducted on dulaglutide, including a clinical trial to evaluate the dosing, efficacy, and safety of dulaglutide in pediatric patients; a study to assess the potential effects on sexual maturation, reproduction, and central nervous system in immature rats; a case registry for at least 15 years to investigate the incidence of medullary thyroid carcinoma in relation to dulaglutide; a trial comparing dulaglutide and insulin glargine in patients with type 2 diabetes and renal impairment; and a cardiovascular outcomes clinical trial in relation to dulaglutide.[9]

Dosing and Administration

Dulaglutide is administered once weekly at any time of the day via subcutaneous injection into the abdomen, thigh, or upper arm.[10] The initial dose of dulaglutide is 0.75 mg administered subcutaneously once weekly. This dose can be increased to 1.5 mg once weekly for additional glycemic control. If a dose is missed, dulaglutide should be administered within 3 days of the missed dose. The day of the weekly administration can be changed if necessary, as long as the last dose was administered ≥3 days before. Dulaglutide can be administered with or without food.[10]

Dulaglutide is available in 2 single-dose pen solutions and in 2 single-dose prefilled syringe solutions for injection—0.75 mg/0.5 mL and 1.5 mg/0.5 mL.[10]

Mechanism of Action

Dulaglutide is a human GLP receptor agonist with 90% amino acid sequence homology to the endogenous human GLP-1 fragment 7-37.[10] Dulaglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor that is coupled to adenylyl cyclase in pancreatic beta cells. By increasing intracellular cyclic adenosine monophosphate in beta cells, dulaglutide leads to glucose-dependent insulin release. Dulaglutide also decreases glucagon secretion and slows gastric emptying.[10]

Clinical Studies

Dulaglutide has been studied as monotherapy and in

Table 1	AWARD-3 Clinical Trial: Dulaglutide Monotherapy versus Metformin, at Week 26		
Efficacy parameter	**Dulaglutide 0.75 mg (N = 270)[a]**	**Dulaglutide 1.5 mg (N = 269)[a]**	**Metformin 1500-2000 mg (N = 268)[a]**
Mean HbA$_{1c}$ level			
Baseline, %	7.6	7.6	7.6
Change from baseline (adjusted mean), %	–0.7	–0.8	–0.6
Mean fasting serum glucose			
Baseline, mg/dL	161	164	161
Change from baseline (adjusted mean), mg/dL	–26	–29	–24
Mean body weight			
Baseline, kg	92.7	92.7	92.4
Change from baseline (adjusted mean), kg	–1.4[b]	–2.3	–2.2

[a]Patients included in the analysis are a subset of the intent-to-treat population who had at least 1 postbaseline assessment; the primary analysis included 265 patients in each of the treatment arms.
[b]Umpierrez G, et al. *Diabetes Care*. 2014;37:2168-2176.
HbA$_{1c}$ indicates glycated hemoglobin.
Source: Trulicity (dulaglutide) injection prescribing information; September 2014.

combination with several antihyperglycemic medications, including metformin, metformin and sulfonylurea, metformin and thiazolidinedione, and prandial insulin with or without metformin.[11,12] These studies evaluated treatment with dulaglutide 0.75 mg and dulaglutide 1.5 mg. Uptitration was not performed in any of the clinical trials. Patients were initiated with dulaglutide 0.75 mg or dulaglutide 1.5 mg, and these doses were maintained for the duration of the clinical trials.[11,12] In patients with type 2 diabetes, dulaglutide was shown to reduce HbA_{1c} levels from baseline compared with placebo.[10] No overall differences in glycemic effectiveness were observed across the demographic subgroups, including age, sex, race and ethnicity, and the duration of diabetes.[10]

AWARD-3: Dulaglutide versus Metformin

The safety and efficacy of dulaglutide monotherapy versus metformin were evaluated in the AWARD-3 trial, a 52-week, double-blind study (26-week primary end point) with 807 patients: the median age was 56 years, and the mean duration of type 2 diabetes was 3 years.[11] All the patients had inadequate glycemic control with diet and exercise, or with diet and exercise and 1 antidiabetic agent used at the submaximal dose.[11]

The patients were randomized to receive dulaglutide 0.75 mg once weekly, dulaglutide 1.5 mg once weekly, or metformin 1500 mg to 2000 mg daily after a 2-week washout period.[11] Approximately 90% of patients who had previously received an antidiabetic agent were receiving metformin at a median dose of 1000 mg daily, and approximately 10% of patients were receiving sulfonylurea.[11]

As shown in **Table 1**, treatment with dulaglutide 0.75 mg or 1.5 mg once weekly resulted in the reduction of HbA_{1c} levels from baseline at the 26-week primary time point. The decrease from baseline in fasting serum glucose levels was similar with dulaglutide 0.75 mg, with dulaglutide 1.5 mg, and with metformin.[11] The decrease in body weight from baseline was similar with dulaglutide 1.5 mg and with metformin, but it was smaller with dulaglutide 0.75 mg compared with metformin. A greater percentage of patients who received dulaglutide 0.75 mg or dulaglutide 1.5 mg reached HbA_{1c} levels of <7.0% and ≤6.5% compared with patients who received metformin (P <.05, all comparisons).[11]

AWARD-5 Trial: Dulaglutide versus Sitagliptin

This 104-week, double-blind, placebo-controlled study (with a 52-week end point) evaluated the safety and efficacy of dulaglutide versus sitagliptin as an add-on therapy to metformin.[10,12] This study included 972 patients; the patients' mean age was 54 years and the mean duration of type 2 diabetes was 7 years. Patients were randomized to receive placebo (after 26 weeks, patients in the placebo

Table 2	AWARD-5 Clinical Trial: Dulaglutide versus Sitagliptin as Add-On Therapy to Metformin, at Week 52		
Efficacy parameter	Dulaglutide 0.75 mg (N = 281)	Dulaglutide 1.5 mg (N = 279)	Sitagliptin 100 mg (N = 273)
Mean HbA_{1c} level			
Baseline, %	8.2	8.1	8.0
Change from baseline (adjusted mean), %	–0.9	–1.1	–0.4
Difference from sitagliptin, %	–0.5 (95% CI, –0.7 to –0.3)[a]	–0.7 (95% CI, –0.9 to –0.5)[a]	
Patients reaching HbA_{1c} <7%, %	49[b]	59[b]	33[b]
Mean fasting plasma glucose			
Baseline, mg/dL	174	173	171
Change from baseline (adjusted mean), mg/dL	–30	–41	–14
Difference from sitagliptin, mg/dL	–15 (95% CI, –22 to –9)	–27 (95% CI, –33 to –20)	
Mean body weight			
Baseline, kg	85.5	86.5	85.8
Change from baseline (adjusted mean), kg	–2.7	–3.1	–1.5
Difference from sitagliptin, kg	–1.2 (95% CI, –1.8 to –0.6)	–1.5 (95% CI, –2.1 to –0.9)	

[a]Multiplicity adjusted 1-sided P <.001.
[b]P <.002 dulaglutide compared with sitagliptin.
CI indicates confidence interval; HbA_{1c}, glycated hemoglobin.
Source: Trulicity (dulaglutide) injection prescribing information; September 2014.

treatment group received blinded sitagliptin 100 mg daily for the remainder of the study), dulaglutide 0.75 mg once weekly, dulaglutide 1.5 mg once weekly, or sitagliptin 100 mg daily, all as add-on therapies to metformin. Randomization occurred after an 11-week lead-in period to allow for a metformin titration period, followed by a 6-week glycemic stabilization period.[10]

Treatment with dulaglutide 0.75 mg and with dulaglutide 1.5 mg once weekly, in combination with metformin, demonstrated a significant reduction in HbA_{1c} levels compared with placebo at 26 weeks, and compared with sitagliptin at 26 weeks and at 52 weeks (**Table 2**).[10,12]

At 26 weeks, the percentage of patients who reached <7.0% HbA_{1c} levels was significantly higher in patients who received dulaglutide 1.5 mg (61%) or dulaglutide 0.75 mg (55%) compared with patients who received sitagliptin (38%; P <.001, for both comparisons).[12] At 52 weeks, the least squares mean changes from baseline in fasting plasma glucose levels were significantly greater with dulaglutide 1.5 mg and with dulaglutide 0.75 mg compared with sitagliptin (P <.001, for both compari-

sons).[12] Furthermore, dulaglutide 0.75 mg and dulaglutide 1.5 mg showed a significantly greater mean change in body weight from baseline at 52 weeks compared with sitagliptin (P <.001, for both comparisons).[12]

Adverse Events

The most common adverse reactions reported in ≥5% of patients who received dulaglutide are nausea, diarrhea, vomiting, abdominal pain, and decreased appetite.[10]

Contraindications

Dulaglutide is contraindicated in patients with a personal history or a family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Dulaglutide should not be used if the patient has a history of serious hypersensitivity to dulaglutide or any of its drug components.[10]

Drug Interactions

Dulaglutide slows gastric emptying and may affect the absorption of concomitantly administered oral drugs.[10]

Warnings and Precautions

Boxed warning. In rodent studies, dulaglutide caused an increase in the incidence of thyroid C-cell tumors after lifetime exposure.[10] It is not known whether dulaglutide causes thyroid C-cell tumors in humans.[10]

Thyroid C-cell tumors in animals. Patients should be counseled about the risk for medullary thyroid carcinoma with the use of dulaglutide.[10]

Pancreatitis. Pancreatitis-related adverse reactions were reported with dulaglutide. Dulaglutide should be promptly discontinued if pancreatitis is suspected and should not be restarted if pancreatitis is confirmed.[10]

Hypoglycemia. Lowering the dose of the sulfonylurea or insulin may be warranted when dulaglutide is used with an insulin secretagogue (eg, sulfonylurea) or insulin to reduce the risk for hypoglycemia.[10]

Hypersensitivity reactions. Dulaglutide should be discontinued if a hypersensitivity reaction is suspected. Patients should be monitored and treated promptly until the signs and symptoms of hypersensitivity resolve.[10]

Renal impairment. Renal impairment should be monitored in patients with renal impairment who report severe adverse gastrointestinal reactions.[10]

Use in Specific Populations

Pregnancy. There are no adequate and well-controlled studies of dulaglutide in pregnant women.[10]

Nursing mothers. It is not known whether dulaglutide is excreted in human milk.[10]

Pediatric use. The safety and efficacy of dulaglutide have not been established in pediatric patients. It is not recommended in young patients aged <18 years.

Geriatric use. No overall differences in the safety or efficacy of dulaglutide were detected between patients aged ≥65 years and younger patients, but greater sensitivity of some older individuals cannot be ruled out.[10]

Hepatic impairment. There is limited experience with dulaglutide in patients with any hepatic impairment.[10]

Renal impairment. No dosage adjustment is recommended for patients with renal impairment. Renal function should be monitored in patients with renal impairment and severe adverse gastrointestinal reactions.[10]

Gastroparesis. Dulaglutide slows gastric emptying.[10]

Conclusion

With the recent FDA approval of dulaglutide, a new, once-weekly subcutaneous injection became available as an adjunct to diet and exercise for adult patients with type 2 diabetes. Dulaglutide, a GLP-1 receptor agonist, provides a once-weekly treatment option that can be used as monotherapy or as an add-on therapy to existing treatment regimens. A once-weekly treatment may provide an attractive option for patients with diabetes.

In 6 clinical studies that included a total of 3342 patients with type 2 diabetes, treatment with dulaglutide resulted in greater reductions from baseline in HbA$_{1c}$ levels compared with placebo, with no overall differences in glycemic reductions across age, sex, race/ethnicity, or duration of disease. ■

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