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Dulaglutide: The Newest GLP-1 Receptor Agonist for the Management of Type 2 Diabetes

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Abstract

Objective: To review the pharmacology, pharmacokinetics, safety, and efficacy of the glucagon-like peptide-1 receptor agonist (GLP-1 RA), dulaglutide, in the treatment of type 2 diabetes mellitus (T2D). **Data Sources:** A PubMed search was completed to identify publications from 1947 to October 2014 using the search terms *dulaglutide* and *LY2189265*. References were reviewed to identify additional resources. **Study Selection and Data Extraction:** Articles were included if they evaluated the pharmacology, pharmacokinetics, safety, or efficacy of dulaglutide. **Data Synthesis:** Dulaglutide reduces both glycosylated hemoglobin (A1C) and weight by stimulating insulin secretion and suppressing glucagon in a glucose-dependent manner, delaying gastric emptying, and promoting satiety. Dulaglutide consists of 2 GLP-1 analogues that have been modified to make it a long-acting, once-weekly agent. Dulaglutide has been studied as monotherapy and in combination with metformin, glimepiride, pioglitazone, and insulin lispro. It has demonstrated superior A1C reduction compared with placebo, metformin, insulin glargine, sitagliptin, and twice-daily exenatide. It demonstrated noninferiority in A1C reduction to liraglutide. Dulaglutide changed A1C by −0.78% to −1.51%, and it changed weight by −0.35 kg to −3.03 kg. The most common adverse effects in clinical studies were nausea, vomiting, and diarrhea. **Conclusions:** Dulaglutide is the fifth GLP-1 RA approved for T2D in the United States. It is an attractive option because it is dosed once-weekly, provides A1C lowering similar to liraglutide, weight reduction similar to exenatide, and has an adverse effect profile similar to exenatide and liraglutide.

Keywords

dulaglutide, GLP-1 receptor agonist, T2D

Introduction

It is estimated that 382 million people worldwide are affected by diabetes.[1] This number is expected to grow to almost 600 million by the year 2035.[1] In the United States, 29.1 million people have diabetes, and in the adult population, type 2 diabetes mellitus (T2D) accounts for at least 90% of these cases.[2] In addition to being a major contributor to cardiovascular disease, kidney failure, blindness, and amputations, diabetes was the seventh leading cause of death in the United States in 2010.[2]

To prevent these complications, guidelines for T2D recommend a patient-centered approach to treatment with metformin and lifestyle modifications as first-line therapy for most individuals.[3-5] Second-line agents consist of sulfonylureas, thiazolidinediones, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), dipeptidyl peptidase-4 (DPP-4) inhibitors, and insulin. Drug characteristics, as well as patient-specific characteristics and preferences, should be considered during the selection of second-line agents. In a systematic review of patient preferences for noninsulin diabetes medications, weight loss and glycemic control were identified as the most important characteristics driving patient preferences regarding diabetes treatment.[6]

The achievement of optimal glycemic control while minimizing adverse events can be difficult with the limited number of treatment options available for T2D; thus, the development of new agents is important. The development of the GLP-1 RAs signified a substantial advancement in the treatment of T2D. GLP-1, an incretin hormone, stimulates insulin secretion and suppresses glucagon secretion in a glucose-dependent manner while delaying gastric emptying and promoting satiety. Whereas native GLP-1 is rapidly

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Table 1. Pharmacokinetic Parameters of Dulaglutide in T2D Patients.

Reference	Cmax (ng/mL)	AUC (ng h/mL)	Vd (L)	Clearance (h)	Half-life (days)
Package insert[9]	114	14 000	17.4	0.107	5
Barrington et al[8]	—	—	13.69	0.107	3.75
Barrington et al[7]	—	—	21.5	0.157	4.96

Abbreviations: AUC, area under the curve; Cmax, maximum concentration; T2D, type 2 diabetes; Vd, volume of distribution.

inactivated by DPP-4, the GLP-1 RAs are modified to resist inactivation by DPP-4 allowing for once- or twice-daily dosing as well as once-weekly dosing. The class of GLP-1 RAs is appealing because these agents lead to weight loss while improving glycemic control, and they have low risk of hypoglycemia.[3] Although the GLP-1 RAs are attractive options as a class, not all GLP-1 RAs are equal, with each having its own distinct pharmacokinetic and pharmacodynamic characteristics based on its molecular size. Changes in glycosylated hemoglobin (A1C), weight, and adverse effects differ when comparing the GLP-1 RAs.

Dulaglutide (Trulicity, Eli Lily) is the most recently approved GLP-1 RA and obtained approval on September 18, 2014. It is administered subcutaneously once weekly with the use of a pen device. The objective of this article is to review the pharmacology, pharmacokinetics, efficacy, and safety of dulaglutide in T2D.

Data Sources

A PubMed search was completed to identify publications in the English language from 1947 to October 2014, using the search terms *dulaglutide* and *LY2189265*. All publications identified were evaluated, and randomized controlled trials including human data were prioritized. References of articles were also reviewed for inclusion if not identified in the PubMed search. Additional data were obtained from published abstracts of phase 3 clinical trial data and the manufacturer. All identified articles describing pharmacology, pharmacokinetics, efficacy, and safety of dulaglutide were evaluated.

Pharmacology

Dulaglutide consists of 2 GLP-1 analogues that have been linked to a human immunoglobulin class 4 constant fragment.[7] This reduces the renal clearance of the drug because of the increased size of the protein (59.7 kDa).[7] The amino acid sequence has been modified in both GLP-1 analogues at positions 8, 22, and 26 to protect the molecule from DPP-4 hydrolysis.[7]

Dulaglutide is a GLP-1 RA that increases insulin secretion and decreases glucagon secretion in a glucose-dependent manner by acting as an incretin mimetic.[8] Dulaglutide also slows gastric motility and promotes satiety. Both preprandial and postprandial blood glucose levels are decreased with the use of dulaglutide.

Pharmacodynamics and Pharmacokinetics

A summary of the pharmacokinetics and pharmacodynamics of subcutaneous dulaglutide can be found in Table 1. Maximum concentrations of dulaglutide are seen at 24 to 72 hours after dosing.[8,9] Steady-state concentrations are achieved after 2 to 4 weeks with once-weekly administration. The site of subcutaneous administration does not change pharmacokinetic properties. Dulaglutide is thought to be broken down into its component amino acids through protein catabolism.[9] No dosage adjustments are recommended based on renal or hepatic dysfunction. Because of the slowing of gastric emptying that occurs with dulaglutide, oral medications with a narrow therapeutic index should be monitored when administered in combination with dulaglutide.[9]

Dose Ranging Studies

The safety, tolerability, pharmacokinetics, and pharmacodynamics of dulaglutide were examined in a phase 1, 3-period, double-blind, placebo-controlled, cross-over study.[8] Doses of 0.1, 0.3, 1, 3, 6, and 12 mg administered subcutaneously were studied as single, escalating doses. Each patient received 2 escalating doses of dulaglutide and 1 dose of placebo. The pharmacokinetic profile of dulaglutide was examined over a 14-day period and can be found in Table 1. Dose-dependent reductions in glucose were seen during a stepped glucose infusion. When dosed at 1 mg or greater, dulaglutide significantly reduced glucose compared with placebo following the oral glucose tolerance test. Reports of adverse effects as well as the duration of gastrointestinal (GI) adverse events increased with increases in dosage. All participants in the dulaglutide 12-mg weekly group experienced vomiting. All 4 serious adverse events (hematemesis, increased blood bilirubin, esophagitis, and gastritis) occurred in a single patient receiving 12 mg weekly of dulaglutide. Compared with placebo, dulaglutide increased heart rate in a dose-dependent fashion; 1.2 bpm in the 0.1 mg group ($P = 0.19$), 3.63 bmp in the 0.3- and 1-mg groups, 6.1 bpm in the 3-mg group, 8.9 bpm in the 6-mg

group, and 15 bpm in the 12-mg group ($P < 0.01$ vs placebo for all doses greater than 0.1 mg).

The pharmacokinetics and pharmacodynamics of dulaglutide were also studied in a placebo-controlled, parallel-group, double-blind study.[7] Patients were assigned to once-weekly doses of 0.05, 0.3, 1, 3, 5, or 8 mg of subcutaneous dulaglutide. The pharmacokinetics of dulaglutide were studied over a 5-week dosing period and can be found in Table 1. Pharmacodynamics were assessed utilizing standardized test meals. Fasting blood glucose was significantly reduced in a dose-dependent fashion, and reductions were significant for all doses except the 0.3-mg dose. Two-hour postprandial blood glucose levels were also reduced compared with placebo for doses of dulaglutide >1 mg ($P < 0.05$ for all doses vs placebo). Changes in glucose levels were observed at 48 hours after the first dose. Gastric emptying was evaluated by determining the absorption of a single dose of acetaminophen elixir given with the solid test meal. These doses were given on day 1 and day 3. Acetaminophen exposure, measured by area under the curve and maximum concentration, was reduced 10% to 60% with the administration of dulaglutide. Only the 5-mg dose demonstrated statistical significance compared with placebo in the least-square-mean ratio of preacetaminophen to postacetaminophen maximum clearance (relative change = 0.41; 90% CI = 0.31, 0.53) and area under the curve (relative change = 0.52; 90% CI = 0.44, 0.62). Nausea, vomiting, diarrhea, and dizziness were the most commonly seen adverse effects, and 94% of patients who experienced vomiting were in the 5- or 8-mg groups. Dulaglutide, at doses greater than 1 mg, significantly increased heart rate in a dose-dependent fashion (1 mg: 3.98 bpm, 90% CI = 0.32, 7.36; 3 mg: 6.85 bpm, 90% CI = 1.72, 11.97; 5 mg: 9.87 bpm, 90% CI = 6.58, 13.17; 8 mg: 8.99 bpm, 90% CI = 5.10-12.89).

Umpierrez et al[10] evaluated the efficacy and safety of dulaglutide in 262 overweight and obese patients. Patients were randomized to 16 weeks of placebo, 4 weeks of dulaglutide 0.5 mg followed by 12 weeks of dulaglutide 1 mg, 16 weeks of dulaglutide 1 mg, or 4 weeks of dulaglutide 1 mg followed by 12 weeks of dulaglutide 2 mg. A1C reduction from baseline compared with placebo was significant for all groups ($P < 0.001$). Compared with placebo, fasting blood glucose was also changed more in all groups (−9, −38, −37, −48 mg/dL, respectively; $P < 0.001$). There was no difference in fasting blood glucose reductions between dulaglutide groups. Glucose response to a test meal was significantly better for each dulaglutide group when compared with placebo, and the dulaglutide 1 mg/2 mg group experienced a significantly better glucose response compared with the other dulaglutide groups ($P < 0.05$). The most common adverse events were nausea, diarrhea, and abdominal distension, and trends indicated more adverse events with higher doses of dulaglutide. Hypoglycemia occurred significantly more in each of the dulaglutide groups compared with placebo at week 4 ($P < 0.05$), and for both groups who were titrated up in dose, rates of hypoglycemia remained significantly higher at week 8 ($P < 0.05$). Heart rate increased compared with placebo for each dulaglutide group (placebo, −1.1 bpm; 0.5/1.0 mg: +3.4 bpm, $P < 0.002$; 1.0/1.0 mg: +1.3 bpm, $P = 0.083$; 1.0/2.0 mg: +4.6 bpm, $P < 0.001$). Because the increase in heart rate typically occurred around the time of dose titration, it is thought that the changes in heart rate were dose dependent.

In a 12-week, double-blind, placebo-controlled study, dose-dependent effects of dulaglutide on glycemic control were studied.[11] Patients were assigned to placebo or dulaglutide 0.1, 0.5, 1, or 1.5 mg subcutaneously weekly. Change in A1C occurred in a dose-dependent fashion, and reduction in A1C was significantly greater than placebo in all groups except the dulaglutide 0.1mg weekly group (least-squares mean difference: −0.37%; $P = 0.069$; −0.89%, −1.04%, −1.04%, respectively; $P < 0.001$). Change in fasting plasma glucose was also greater compared with placebo for all dosing groups except for dulaglutide 0.1 mg weekly. Average mean fasting and postmeal plasma glucose levels were reduced in a dose-dependent manner for patients treated with dulaglutide ($P \leq 0.003$). About half of all patients experienced at least 1 treatment-associated adverse event; however, no dose-related trends were seen.

Terauchi et al[12] conducted a randomized, double-blind, placebo-controlled, parallel-group, 12-week study to compare 3 doses of dulaglutide in 145 Japanese patients.[12] Patients were randomized to placebo or dulaglutide 0.25, 0.5, or 0.75 mg subcutaneously weekly. Significant dose-dependent improvements were seen in A1C, fasting blood glucose, and postmeal glucose for all groups when compared with placebo. The least-squares mean difference in A1C compared with placebo was −0.72%, −0.97%, and −1.17%, respectively; $P < 0.01$. The least-squares mean difference in fasting blood glucose compared with placebo was −20.2, −19.65, and −28.5 mg/dL, respectively; $P < 0.001$. Approximately 45% of patients experienced a treatment-related adverse event; however, no dose-related trends were seen.

The use of dulaglutide was evaluated in patients with renal or hepatic impairment in 2 open-label studies of dulaglutide 1.5 mg weekly.[13] Area under the curve and maximum concentrations were <30% greater in patients with renal impairment than in patients without renal impairment. No changes in pharmacokinetic parameters were found with changes in glomerular filtration rate. In patients with hepatic impairment, there was lower exposure than in patients without hepatic impairment. Degree of hepatic impairment was not proportional to exposure, however. Overall, no changes in safety parameters were seen in patients with renal or hepatic impairment; however, because of the limited number of patients with renal or hepatic dysfunction studied, caution should be used in these patient populations.[9]

Based on the efficacy and safety results of the pharmacokinetic and pharmacodynamic dose-finding studies, phase 3 clinical trials focused on 0.75- and 1.5-mg weekly doses.

Table 2. Summary of Randomized Controlled Trials of Dulaglutide in Type 2 Diabetes.

Citation	Design	Baseline Characteristics	Background Treatment	Randomly Assigned Treatment	Change in A1C From BL, Percentage (SD)	Change in Weight From BL, kg (SD)
Wysham et al (AWARD-1)[17]	Open label, superiority,[a] noninferiority; 26 weeks, n = 978	Mean age, 56 years; A1C, 8.1%; BMI, 33 kg/m^2; duration of diabetes, 9 years	Metformin 1500-3000 mg + pioglitazone 30-45 mg	Dulaglutide 1.5 mg	−1.51 (0.06)	−1.3 (0.29)
				Dulaglutide 0.75 mg	−1.30 (0.06)	+0.2 (0.29)
				Exenatide 10 µg bid	−0.99 (0.06)	−1.07 (0.29)
				Placebo	−0.46 (0.08)	+1.24 (0.37)
Giorgino et al (AWARD-2)[18,b]	Open-label, noninferiority, 78 weeks, n = 807	Mean age, 57 years; A1C, 8.1%; weight, 86.3 kg; BMI NR, duration of diabetes NR	Metformin ≤1500 mg + glimepiride ≥4 mg	Dulaglutide 1.5 mg	−0.90 (0.07)	−1.96 (0.26)
				Dulaglutide 0.75 mg	−0.62 (0.07)	−1.54 (0.26)
				Insulin glargine[c]	−0.59 (0.07)	+1.28 (0.26)
Umpierrez et al (AWARD-3)[14]	Double-blind, noninferiority, 26 weeks, n = 807	Mean age, 56 years; A1C, 7.6%; BMI, 33 kg/m^2; duration of diabetes, 3 years	None	Dulaglutide 1.5 mg	−0.78 (0.06)	−2.29 (0.24)
				Dulaglutide 0.75 mg	−0.71 (0.06)	−1.36 (0.24)
				Metformin 1500-2000 mg	−0.56 (0.06)	−2.22 (0.24)
Jendle et al (AWARD-4)[19,b]	Open-label, noninferiority, 52 weeks, n = 884	Mean age, 59.4 years; A1C, 8.5%; BMI, 32.5 kg/m^2; duration of diabetes, 13 years	Insulin lispro ± metformin ≥ 1500 mg	Dulaglutide 1.5 mg	−1.48 (0.08)	−0.35 (0.34)
				Dulaglutide 0.75 mg	−1.42 (0.08)	+0.86 (0.33)
				Insulin glargine[c]	−1.23 (0.08)	+2.89 (0.33)
Nauck et al (AWARD-5)[15]	Double-blind, noninferiority, 52 weeks, n = 1098	Mean age, 54 years; A1C, 8.1%; BMI, 31 kg/m^2; duration of diabetes, 7 years	Metformin ≥1500 mg	Dulaglutide 1.5 mg	−1.1 (0.06)	−3.03 (0.22)
				Dulaglutide 0.75 mg	−0.87 (0.06)	−2.60 (0.22)
				Sitagliptin 100 mg	−0.39 (0.06)	−1.53 (0.22)
Dungan et al (AWARD-6)[16]	Open-label, noninferiority, 26 weeks, n = 599	Mean age, 56.7 years; A1C, 8.1%; BMI, 33.6 kg/m^2; duration of diabetes, 7.2 years	Metformin ≥1500 mg	Dulaglutide 1.5 mg	−1.42 (0.05)	−2.90 (0.22)
				Liraglutide 1.8 mg	−1.36 (0.05)	−3.61 (0.22)

Abbreviations: AC, active comparator; A1C, glycosylated hemoglobin; BL, baseline; BMI, body mass index; NR, not reported.
[a]Superiority testing versus placebo; noninferiority testing versus active comparator.
[b]Abstract only.
[c]Dose uptitrated as needed based on prespecified criteria.

Clinical Trials

Six randomized controlled trials (AWARD 1-6) were the foundation for the Food and Drug Administration (FDA) approval of dulaglutide. The AWARD studies evaluated dulaglutide 1.5- and 0.75-mg weekly in more than 5000 patients. In one study, patients were not receiving any background treatment.[14] In all other trials, patients were receiving metformin alone[15,16] or in combination with pioglitazone,[17] glimepiride,[18] or insulin lispro.[19] Dulaglutide has been compared with placebo,[17] exenatide,[17] insulin glargine,[18,19] metformin,[14] sitagliptin,[15] and liraglutide.[16] In the AWARD studies, mean baseline A1C ranged from 7.6% to 8.5% and was most commonly 8.1%. A summary of the AWARD studies can be found in Table 2. The AWARD 2 and AWARD 4 studies are only available in abstract form.

Monotherapy

The AWARD 3 study examined patients with early-stage T2D and a baseline A1C of 7.6% who were uncontrolled on lifestyle modifications or a single oral diabetes medication at <50% of the maximum dose. Patients who had taken a GLP-1 RA or a thiazolidinedione in the past 3 months or had received chronic insulin therapy were excluded. All oral diabetes medications were discontinued for a 2-week washout period. Patients experienced a greater change in A1C with both dulaglutide 1.5 mg (−0.78%) and dulaglutide 0.75 mg (−0.71%) when compared with metformin 1500 to 2000 mg daily (−0.56%; $P = 0.002$ and 0.02, respectively).[14] This difference in A1C reduction was sustained for the entire 52-week study. More patients in both dulaglutide groups achieved A1C targets of <7% compared with metformin. In all, 62% of patients in the dulaglutide group achieved an A1C <7%, and 63% of patients in the dulaglutide 0.75mg weekly group achieved this goal. Only 54% of patients in the metformin group achieved an A1C <7% ($P = 0.02$ for both comparisons). Weight change was similar between dulaglutide 1.5 mg and metformin at 26 weeks. (−2.29 vs −2.22 kg; P not significant [NS]). Weight change was less with dulaglutide 0.75 mg compared to metformin. (−1.36 vs −2.22 kg; $P = 0.003$). Differences in weight reduction remained consistent throughout the 52-week study period.

Add-on Therapy Versus Active Comparator

In the AWARD 1 study, patients with a baseline A1C of 8.1% on metformin (1500-3000 mg daily) and pioglitazone (30-45 mg daily) experienced a superior reduction in A1C with both dulaglutide 1.5 mg and dulaglutide 0.75 mg when compared with exenatide 10 µg twice daily and placebo.[17]

At 26 weeks, a greater A1C change was seen with dulaglutide 1.5 mg compared with exenatide and placebo (−1.51%, −0.99%, −0.46%; $P < 0.001$ for both comparisons). A greater A1C change was seen with dulaglutide 0.75 mg compared with exenatide and placebo (−1.30%, −0.99%, −0.46%; $P < 0.001$ for both comparisons). More patients in both dulaglutide groups (1.5- and 0.75-mg) achieved an A1C target of less than 7% compared with those in the exenatide and placebo groups over the 52-week study period. (78%, 66%, 52%, and 43%, respectively; $P < 0.001$ for all comparisons). Weight change was significantly better for patients in both dulaglutide 1.5 mg and dulaglutide 0.75 mg compared with patients in the placebo group (−1.30, +0.20, +1.24 kg, $P < 0.001$, and $P < 0.010$, respectively). Patients taking exenatide (−1.07kg) experienced more weight loss than patients taking dulaglutide 0.75 mg (+0.2 kg, $P < 0.001$) and similar weight loss compared with patients taking dulaglutide 1.5 mg (−1.30 kg; P = NS).

The phase 3, open-label, randomized AWARD 2 study compared dulaglutide 1.5- and 0.75- mg with insulin glargine titrated to a target fasting blood glucose <100 mg/dL in patients treated with metformin (≥1500 mg daily) and glimepiride (≥4 mg daily).[18] At 78 weeks, dulaglutide 1.5 mg was superior to insulin glargine in A1C reduction, with dulaglutide lowering A1C by 0.9% and insulin glargine lowering A1C by 0.62% ($P < 0.001$). Dulaglutide 0.75 mg weekly was noninferior to insulin glargine, lowering A1C by 0.59% ($P_{\text{noninferiority}} < 0.001$). Patients in the dulaglutide 1.5mg weekly group experienced 1.96 kg weight loss, and patients in the dulaglutide 0.75mg weekly group experienced 1.54 kg weight loss. Patients in the insulin glargine group gained an average of 1.28 kg ($P < 0.001$ for both comparisons). For patient-reported outcomes, dulaglutide, when compared with insulin glargine, significantly improved the ability to perform physical activities of daily living, the impact of weight on self-perception, and the low blood sugar survey behavior and worry measures ($P < 0.05$ for all measures).

Dulaglutide was compared with insulin glargine in the AWARD 4 study.[19] Patients having uncontrolled readings, with an average baseline A1C of 8.5% on insulin lispro ± metformin (1500 mg daily), were included. At 52 weeks, change in A1C from baseline was statistically better for both dulaglutide 1.5 mg and 0.75 mg compared with insulin glargine dosed following a treat-to-target dosing algorithm (−1.48%, −1.42%, −1.23%, respectively; $P < 0.02$ for both comparisons). At 26 and 52 weeks, more patients in the dulaglutide 1.5- and 0.75-mg groups achieved an A1C <7% compared with patients taking insulin glargine (26 weeks: 67.6%, 69%, 56.8%; $P < 0.05$; 52 weeks: 58.5%, 56.3%, 49.3%; $P < 0.05$). Patients in the dulaglutide 1.5 mg weekly group lost an average of 0.35 kg, and patients in the dulaglutide 0.75 mg weekly and insulin glargine groups gained weight (0.86 and 2.89 kg, respectively). Significantly more weight was gained in patients taking insulin glargine than patients in either dulaglutide group ($P < 0.05$).

The AWARD 5 study compared dulaglutide with the DPP-4 inhibitor sitagliptin 100 mg daily and included patients with a baseline A1C of 8.1% treated with metformin monotherapy (≥1500 mg daily).[15] Patients in the dulaglutide 1.5 mg and 0.75 mg arms experienced a superior reduction in A1C compared with patients in the sitagliptin and placebo arms. At 52 weeks, A1C change was superior for dulaglutide 1.5- and 0.75- mg compared with sitagliptin (−1.10%, −0.87%, −0.39%; $P < 0.001$ for both comparisons). Significantly more patients achieved an A1C target <7% at 52 weeks in the dulaglutide 1.5- and 0.75- mg arms compared with the sitagliptin arm (58%, 49%, 33%; $P < 0.001$ for both comparisons). Weight change was significantly greater for patients in both the dulaglutide 1.5 mg and dulaglutide 0.75 mg groups compared with patients in the sitagliptin group (−3.30, −2.60, −1.53 kg; $P < 0.001$ for both comparisons).

The AWARD 6 study compared dulaglutide 1.5 mg weekly with liraglutide 1.8 mg daily in uncontrolled T2D patients with a baseline A1C of 8.1% on metformin therapy (≥1500 mg daily).[16] At 26 weeks, dulaglutide 1.5 mg weekly was noninferior, but not superior, to liraglutide 1.8 mg daily. Reduction in A1C from baseline was 1.42% for the dulaglutide arm and 1.36% for the liraglutide arm ($P_{\text{noninferiority}} < 0.0001$). A target A1C was achieved in 68% of patients in both the dulaglutide and liraglutide groups. Significantly less weight loss was seen with dulaglutide when compared with liraglutide, with a 2.6 kg reduction in the dulaglutide arm and a 3.61 kg reduction in the liraglutide arm ($P = 0.011$). The AWARD-6 study also examined patient-reported outcomes. Both groups had significant improvements in impact of weight on self-perception, with no between group differences. The dulaglutide group also had significant improvements from baseline in ability to perform physical activities of daily living ($P = 0.014$) and quality of life ($P = 0.031$).

Dosage and Administration Recommendations

Dulaglutide is administered once-weekly at any time of day, without regard to meals.[9,20] The drug should be injected subcutaneously into the abdomen, thigh, or upper arm.[20] The initial starting dose is 0.75 mg once weekly. The dose can be increased to 1. 5 mg once weekly if additional glycemic control is needed. Missed doses should be administered within 3 days of the missed dose. No dose adjustments are needed in patients with renal impairment, including end-stage renal disease.[9] The medication comes as a 0.75 mg/0.5 mL or 1.5 mg/0.5 mL solution in a single-dose pen or prefilled syringe.[9,20] The disposable, prefilled, single-use pen device is supplied with a needle attached and does not

Table 3. Adverse Events Across Randomized Controlled Trials of Dulaglutide in Type 2 Diabetes.

Study	Randomly Assigned Treatment	Nausea (%)	Vomiting (%)	Diarrhea (%)	Symptomatic Hypoglycemia (%)	Severe Hypoglycemia (n)	Discontinuation Because of AE (%)
Wysham et al (AWARD-1)[17]	Dulaglutide 1.5mg	28[a]	17[a,b]	11	10.4	0	3
	Dulaglutide 0.75 mg	16[a,b]	6[a,b]	8	10.7	0	1
	Exenatide 10 µg bid	26[a]	11[a]	6	15.9	2	3
	Placebo	6	1	6	3.5	0	2
Giorgino et al (AWARD-2)[18,c]	Dulaglutide 1.5mg	15.4[b]	NR	10.6[b]	1.7[b,d]	NR	NR
	Dulaglutide 0.75 mg	7.7[b]		9.2[b]	1.7[b d]		
	Insulin glargine	1.5		5.7	3.0[d]		
Umpierrez et al (AWARD-3)[14]	Dulaglutide 1.5mg	19	8.6	10	12.3	0	4.8
	Dulaglutide 0.75mg	10.7	5.9	5.2[b]	11.1	0	2.2
	Metformin 1500-2000 mg	14.6	4.1	13.8	12.7	0	3.7
Jendle et al (AWARD-4)[19,c]	Dulaglutide 1.5 mg	25.8[b]	NR	16.6[b]	31[d]	11	NR
	Dulaglutide 0.75 mg	17.7[b]		15.7[b]	35[d]	15	
	Insulin glargine	3.4		6.1	39.9[d]	22	
Nauck et al (AWARD-5)[15]	Dulaglutide 1.5 mg	17[b]	13[b]	15[b]	10.2	0	10.9
	Dulaglutide 0.75 mg	14[b]	8[b]	10[b]	5.3	0	7.6
	Sitagliptin 100 mg	5	2	3	4.8	0	9.5
Dungan et al (AWARD-6)[16]	Dulaglutide 1.5 mg	20	7	12	9	0	6
	Liraglutide 1.8 mg	18	8	12	6	0	6

[a]$P < 0.05$ versus placebo.
[b]$P < 0.05$ versus active comparator.
[c]Abstract only.
[d]Reported as events/patient/year.
Abbreviations: AE, adverse events; NR, not reported.

require reconstitution. Specific administration techniques should be used when administering dulaglutide with the pen device. The pen should be stored in the refrigerator but can be stored at room temperature for up to 14 days.[20]

Adverse Effects/Safety

A summary of adverse events can be found in Table 3. Adverse effects of dulaglutide are comparable with those of other GLP-1 inhibitors, with nausea, vomiting, and diarrhea being the most commonly reported side effects. Adverse events were mostly mild to moderate and transient in nature.[8,14-19]

In the 6 landmark trials used for the approval of dulaglutide, rates of nausea ranged from 15.4% to 28% in the dulaglutide 1.5 mg group and 7.7% to 17.7% in the dulaglutide 0.75 mg group.[14-19] Vomiting was less common, occurring in 7% to 17% of patients in the dulaglutide 1.5 mg group and 5.9% to 10.6% in the dulaglutide 0.75 mg group. Diarrhea occurred in 10% to 16.6% of patients in the high-dosing regimen and 5.2% to 15.7% of patients in the lower-dosing regimen. In one dulaglutide dose-finding study, the majority of patients who experienced GI adverse events experienced these events after the first dose of dulaglutide.[7]

In the AWARD trials, nausea, vomiting and diarrhea were all significantly more common in patients taking dulaglutide 1.5 and 0.75 mg compared with placebo (Table 3).[14-19] Compared with metformin, dulaglutide resulted in similar rates of GI adverse events; however, significantly more diarrhea occurred in patients on metformin compared with dulaglutide 0.75 mg.[17] GI adverse events were more common in patients taking dulaglutide than in those taking sitagliptin and insulin glargine.[15,18,19] Compared with exenatide, GI adverse events were more common with the dulaglutide 1.5 mg dose but less common with the 0.75 mg dose.[17] The AWARD 6 study found no significant differences in GI adverse events between dulaglutide and liraglutide.[16]

The incidence of hypoglycemia was minimal across all studies. In the AWARD 1 study, hypoglycemia occurred less frequently in patients randomized to dulaglutide compared with those randomized to exenatide (10.4 vs 15.9%; $P = 0.007$).[17] Hypoglycemia occurred more frequently in the dulaglutide 1.5 mg and 0.75 mg groups compared with the placebo group (10.4%, 10.7%, 3.5%, respectively; *P*, not reported). Rates of hypoglycemia were lower in patients taking dulaglutide compared with patients taking insulin glargine in the AWARD 2 study (1.7 vs 3 events/patient/year; $P < 0.05$), and rates of hypoglycemia were lower for patients on dulaglutide compared with patients treated with insulin glargine in the AWARD 4 study (31 vs 40 events/patient/year; *P*, not reported).[19] Incidence of hypoglycemia was similar when comparing dulaglutide with metformin in the AWARD 3 study.[14] Rates of hypoglycemia in the AWARD 5 study were 10.2% for dulaglutide and 4.8% for sitagliptin (*P*, not reported), and rates of hypoglycemia in the AWARD 6 study were 9% and 6% for dulaglutide and liraglutide, respectively (*P*, not reported).[15,16] Overall, rates

of hypoglycemia with dulaglutide were higher in the AWARD trials that included background therapies known to cause hypoglycemia, such as insulin and sulfonylureas.

GLP-1 RAs have been shown to reduce systolic blood pressure and increase heart rate.[21] A 16-week, randomized, double-blind, multicenter, placebo-controlled study examined the effects of dulaglutide on blood pressure and heart rate compared with placebo.[22] Dulaglutide 1.5 mg weekly was found to significantly reduce systolic blood pressure compared with placebo (least squares mean = −2.8 mm Hg; $P \leq 0.001$) and significantly increase heart rate compared with placebo (least squares mean = 2.8 bpm; $P < 0.05$). In the AWARD trials, no significant differences were seen in heart rate or blood pressure when comparing dulaglutide with liraglutide and metformin. At 52 weeks, there was no difference in heart rate or blood pressure when comparing dulaglutide with exenatide. After 52 weeks of therapy, dulaglutide 1.5- and 0.75- mg did result in an increase in heart rate compared with sitagliptin (+2.4, +2.1, −0.3 bpm, respectively; $P < 0.001$). The clinical significance of these findings is unknown.

There are no trials evaluating the use of dulaglutide in pregnancy. In rats and rabbits, the use of dulaglutide led to reductions in fetal growth, skeletal abnormalities, and ossification deficits, likely from decreased maternal intake and weight during pregnancy.[9] Dulaglutide is a pregnancy category C medication. It is unknown if dulaglutide is passed through breast milk, and it is recommended that mothers not nurse while taking dulaglutide.[9]

Increases in pancreatic enzymes did occur in patients taking dulaglutide; however, only 1 patient developed pancreatitis while taking dulaglutide during the 4 published AWARD trials.[17] In phase 2 and 3 clinical studies, a total of 12 patients receiving dulaglutide experienced a pancreatitis-related adverse event.[9] In patients receiving nonincretin agents, 3 developed pancreatitis-related adverse events. Confirmed pancreatitis occurred in 5 patients taking dulaglutide and in 1 patient taking a nonincretin agent. Patients taking dulaglutide should be monitored for pancreatitis, and if pancreatitis develops, it should be discontinued. Dulaglutide has not been studied in patients with a history of pancreatitis.[9] The FDA has required the inclusion of this risk in the Risk Evaluation and Mitigation Strategy (REMS) program for dulaglutide, cautioning about this potential adverse effect.[9,23]

The REMS program for dulaglutide also cautions patients and providers about the potential for thyroid c-cell tumors. Similar to other GLP-1 RAs, the FDA also required a black box warning of potential thyroid c-cell tumors for dulaglutide. Thyroid c-cell tumors have occurred in rats exposed to dulaglutide in a dose-related and treatment duration–dependent manner. One case of thyroid c-cell carcinoma occurred in a patient exposed to dulaglutide. This patient had elevated levels of calcitonin prior to exposure to dulaglutide.[9,23]

Postmarketing requirements for Eli Lily, the manufacturer of dulaglutide, include the evaluation of dulaglutide in pediatric patients; the effects of the drug on sexual maturation, reproduction, and central nervous system development in rats; a case registry of at least 15 years to further evaluate the risk of medullary thyroid carcinoma; comparison of dulaglutide to insulin glargine in patients with moderate to severe renal impairment; and the cardiovascular risks of the agent.[24]

Formulary Considerations

There are no current studies examining the cost-effectiveness of the clinical use of dulaglutide. Although dulaglutide is FDA approved, it was just made available in pharmacies throughout the United States in early November 2014. Although the exact cost of dulaglutide will depend on insurance coverage and pharmacy pricing, it will likely be priced similarly to liraglutide but higher than albiglutide. A discount card is available through Eli Lilly for a maximum of 2 years. GLP-1 RAs are attractive options because they provide glycemic control and weight loss with minimal hypoglycemia. Disadvantages of GLP-1 RAs are that they may cause GI adverse effects, are expensive, and are injectable. As a GLP-1 RA, dulaglutide is a viable second-line option with demonstrated superior efficacy to other second-line agents, including the DPP-4 inhibitor sitagliptin and insulin glargine, for the treatment of T2D in patients who are uncontrolled with or cannot tolerate first-line metformin.

When deciding on the inclusion or exclusion of dulaglutide on a formulary, the differences in the GLP-1RAs must be considered. In the United States, there are several GLP-1 RAs to choose from, including twice-daily exenatide (Byetta), once-weekly exenatide (Bydureon), once-daily liraglutide (Victoza), once-weekly albiglutide (Tanzeum), and once-weekly dulaglutide (Trulicity).

Studies comparing the GLP-1 RAs head to head have shown that twice-daily exenatide is less effective at glucose lowering compared with once-weekly exenatide and liraglutide. It also results in more GI adverse effects than once-weekly exenatide and liraglutide.[25-27] Liraglutide has better glucose-lowering effects but higher rates of GI adverse events when compared with once-weekly exenatide.[28] When compared with liraglutide, albiglutide was associated with less glucose lowering and less weight loss; however, fewer GI adverse effects occurred with albiglutide.[29]

Dulaglutide resulted in greater glucose lowering and similar weight loss compared with twice-daily exenatide. Rates of GI adverse events were similar for both agents.[17] Compared with liraglutide, dulaglutide produced similar glucose-lowering effects and similar GI effects but less weight loss.[16] Although 2 approved dosages of dulaglutide have been compared with several other T2D agents, the comparison of these 2 doses must also be considered. Dulaglutide 1.5 mg weekly demonstrated the best efficacy

in terms of A1C reduction and weight loss. However, these advantages come at the expense of increased adverse events.

Dulaglutide offers the advantage of being a once-weekly medication, but it has not been compared in head-to-head studies with the other 2 once-weekly GLP-1 RAs. Dulaglutide is an attractive GLP-1 RA offering once-weekly dosing with glucose lowering similar to liraglutide, weight loss similar to twice-daily exenatide, and GI adverse effects similar to both liraglutide and exenatide. Cost will also be an important consideration when considering the addition of dulaglutide to a formulary once this information is more readily available in the United States.

Conclusion

With the approval of dulaglutide, providers now have another GLP-1 RA available for the treatment of T2D. During the 6 landmark studies for dulaglutide, the drug reduced A1C by 0.78% to 1.51%, and it reduced weight by 0.35 to 3.03 kg. Major side effects of dulaglutide are consistent with those of other GLP-1 RAs and consist of nausea, vomiting, and diarrhea. Dulaglutide demonstrated superior A1C reduction compared with placebo, metformin, insulin glargine, sitagliptin, and the GLP-1 RA exenatide twice-daily. It was noninferior to the GLP-1 RA, liraglutide, for A1C reduction. Dulaglutide is an attractive GLP-1 RA option to treat T2D, with demonstrated glycemic and weight benefits, acceptable tolerability and safety, and once-weekly dosing.

Declaration of Conflicting Interests

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