**MECHANISM OF ACTION**

The primary mechanism of action of dulaglutide, as an incretin mimetic hormone or an analogue of human glucagon-like peptide-1, is to increase insulin secretion when glucose levels are elevated, decrease glucagon secretion, and delay gastric emptying in an effort to lower postprandial glucose level. Dulaglutide also activates the membrane-bound cell-surface receptor in pancreatic beta cells known as the GLP-1 receptor.

**PHARMACODYNAMICS**

After a single dose, dulaglutide has the ability to decrease fasting glucose levels and reduce postprandial glucose concentrations in type-2 diabetes patients.

**Fasting and Postprandial Glucose**

In a study of adults with type-2 diabetes mellitus, treatment with once-weekly dulaglutide resulted in a reduction of fasting and two-hour postprandial glucose concentrations, and postprandial serum glucose incremental area under the curve (AUC), when compared to placebo (−25.6 mg/dL, −59.5 mg/dL, and −197 mg/h/dL, respectively); these effects were sustained after six weeks of the 1.5-mg dose.

**First- and Second-Phase Insulin Secretion**

In type-2 diabetic patients who were treated with dulaglutide, both first- and second-phase insulin secretions increased when compared with placebo.

**Insulin and Glucagon Secretion**

Dulaglutide reduces glucagon secretion and prompts glucose-dependent insulin secretion. When patients were treated with dulaglutide 0.75 mg and 1.5 mg once weekly, their fasting insulin increased from baseline at week 26 by 35.38 and 17.50 pmol/L, respectively, and C-peptide concentration by 0.09 and 0.07 nmol/L, respectively, in a phase 3 monotherapy study.
study. In the aforementioned study, fasting glucagon concentrations were also reduced by 1.71 and 2.05 pmol/L from baseline.\textsuperscript{5}

**Gastric Motility**

Dulaglutide delays gastric emptying, with the largest delay occurring after the first dose and then lessening with succeeding doses.\textsuperscript{5}

**Cardiac Electrophysiology (QTc)**

In a QTc study utilized to determine the effect of dulaglutide on cardiac repolarization, dulaglutide did not produce QTc prolongation.\textsuperscript{5}

### PHARMACOKINETICS

The pharmacokinetics of dulaglutide can be seen following subcutaneous administration. The time to maximum concentration at steady state ranges from 24 to 72 hours, with a median of 48 hours. Steady-state concentrations were achieved between two and four weeks after once-weekly administration. After multiple-dose administration of 1.5 mg to steady state, the mean peak plasma concentration and total systemic exposure (AUC) of dulaglutide were 114 ng/mL and 14,000 ng•h/mL. The accumulation ratio was approximately 1.56.\textsuperscript{5} There was no statistically significant effect based on exposure sites.\textsuperscript{5}

**Absorption and Distribution**

The mean absolute bioavailability of single 0.75-mg and 1.5-mg doses of dulaglutide was 65% and 47%, respectively.\textsuperscript{5} The mean volumes of distribution were approximately 19.2 L and 17.4 L, respectively.\textsuperscript{5}

**Metabolism and Elimination**

It is assumed that dulaglutide is degraded into its component amino acids upon administration.\textsuperscript{5} However, at steady state, the mean apparent clearance is approximately 0.111 L per hour for the 0.75-mg dose and 0.107 L per hour for the 1.5-mg dose. The elimination half-life of dulaglutide for both doses is approximately five days.\textsuperscript{5} As with most medications in the class, dulaglutide should be used with caution, and both renal and hepatic function should be monitored. Nevertheless, dulaglutide does not require dose adjustments.

### PIVOTAL CLINICAL TRIALS

The FDA’s approval of dulaglutide was based on a combination of studies. The trials evaluated the use of dulaglutide 0.75 mg and 1.5 mg.\textsuperscript{7} Uptitration of dulaglutide was not performed in any of the trials; patients were initiated and maintained on either 0.75 mg or 1.5 mg for their duration.\textsuperscript{3} In patients with type-2 diabetes mellitus, dulaglutide produced reductions from baseline in hemoglobin A1c (HbA1c) compared to placebo. No overall differences in glycemic effectiveness were observed across demographic subgroups (age, gender, race/ethnicity, or duration of diabetes).\textsuperscript{5}

**Monotherapy Trials**

**Wysham and colleagues**

Wysham and colleagues conducted a 52-week, multicenter, parallel-arm study that randomized patients to dulaglutide 0.75 mg, dulaglutide 1.5 mg, exenatide 10 mcg, or placebo. This study included both men and women who were at least 18 years of age with a body mass index between 23 and 45 kg/m\textsuperscript{2} and an HbA1c between 7% and 11%. Patients also had to be on an oral antihyperglycemic medication (OAM) as monotherapy.\textsuperscript{8}

Eligible patients were treated with metformin (1,500–3,000 mg) and pioglitazone (30–45 mg). Over a period of 12 weeks prior to the study, previous OAMs other than metformin and pioglitazone were discontinued. Patients were then titrated on a dual-OAM regimen of maximum tolerated metformin and pioglitazone.\textsuperscript{8} After patients were stabilized prior to randomization, their HbA1c had to be greater than 6.5% to maintain eligibility. All eligible patients were then randomized to one of four arms.\textsuperscript{9}

The mean age of patients was 56 years with a mean duration of type-2 diabetes of three years. Forty-four percent were male. Patients were 74% white, 7% black, and 8% Asian, and 29% of the study population was in the U.S.\textsuperscript{8}

Exenatide patients received 5 mcg twice a day for the first four weeks and 10 mcg twice a day for the remainder of the study. At 26 weeks, placebo-treated patients were then switched in a blinded fashion to either dulaglutide 1.5 mg or dulaglutide 0.75 mg.\textsuperscript{5}

Treatment with dulaglutide 0.75 mg and 1.5 mg once weekly resulted in a reduction in HbA1c (1.3% and 1.5%) compared to placebo (0.5%) and compared to exenatide (1.0%) at 26 weeks. During the 52-week study, 8.9% of patients required glycemic rescue in the dulaglutide 0.75 mg plus metformin and pioglitazone treatment group, 3.2% in the dulaglutide 1.5 mg once weekly plus metformin and pioglitazone treatment group, and 8.7% in the exenatide twice a day plus metformin and pioglitazone treatment group.\textsuperscript{5}

**Umpierrez et al.**

Umpierrez and colleagues conducted a 52-week double-blind study to compare the efficacy and safety of monotherapy with dulaglutide to metformin-treated patients with type-2 diabetes mellitus. Patients were randomized to receive dulaglutide 0.75 mg, dulaglutide 1.5 mg, or metformin 1,500–2,000 mg per day.\textsuperscript{9} Patients were included in the study if their HbA1c was lower than 9.1% but higher than 6.5% with lifestyle modification or low-dose OAM monotherapy.\textsuperscript{9}

Reductions in HbA1c were noted at 26 weeks. Dulaglutide 0.75 mg showed a reduction of 0.71% ± 0.06%, dulaglutide 1.5 mg showed a reduction of 0.78% ± 0.06%, and metformin showed a reduction of 0.56% ± 0.06%, demonstrating that both dulaglutide 0.75 mg and dulaglutide 1.5 mg were superior to metformin.\textsuperscript{9} No severe hyperglycemia was reported during the study, and weight loss was similar to that of metformin in both dulaglutide groups. The most common adverse effects seen over the 52-week period were nausea, diarrhea, and vomiting.\textsuperscript{6} Overall, dulaglutide improved the glycemic control of patients and demonstrated the ability to be well tolerated as monotherapy in patients with early-stage type-2 diabetes.

**Combination Therapy Trial**

**Nauck et al.**

In this 104-week, multicenter, double-blind, parallel-arm study, Nauck and colleagues compared the efficacy and safety of two doses of once-weekly dulaglutide to sitagliptin in uncontrolled, metformin-treated patients with type-2 diabetes. This study included 1,098 randomized patients with an average age of 54 years; an average HbA1c of 8.1%; an average weight of 86.4 kg; and diabetes for an average of seven years.\textsuperscript{3} Patients received either dulaglutide 0.75 mg once weekly, dulaglutide 1.5 mg once weekly, sitagliptin 100 mg per day, or placebo.\textsuperscript{10} The average HbA1c reductions...
were \(-1.10 \pm 0.06\), \(-0.87 \pm 0.06\), and \(-0.39 \pm 0.06\) for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and sitagliptin.10 Both dulaglutide doses were superior to sitagliptin. During the study, the most common adverse events were nausea, diarrhea, and vomiting with both doses of dulaglutide.10

In conclusion, treatment with dulaglutide 0.75 mg and 1.5 mg once weekly resulted in a statistically significant reduction in HbA1c compared to placebo at 26 weeks and compared to sitagliptin at both 26 and 52 weeks, all of which were in combination with metformin.

ADVERSE EFFECTS
At baseline, 2.5% of the population reported retinopathy, and baseline estimated renal function was normal or mildly impaired (estimated glomerular filtration rate 60 mL/min/1.73 m² or higher) in 96% of the pooled study populations.5 Adverse reactions were not present at baseline, occurred more commonly on dulaglutide than on placebo, and occurred in at least 5% of patients treated with dulaglutide.5 The most common adverse reactions to dulaglutide reported in 5% or more of patients included nausea, diarrhea, vomiting, abdominal pain, decreased appetite, dyspepsia, and fatigue. Other adverse reactions include hypoglycemia, tachycardia, immunogenicity, hypersensitivity, injection-site reactions, PR interval prolongation and first-degree atrioventricular block, and amylase and lipase increase.5

DRUG INTERACTIONS
Monitoring and caution should be employed when oral medications are concomitantly administered with dulaglutide because it slows gastric emptying and thus has the potential to reduce the rate of absorption of concomitantly administered oral medications.5 Drug levels of oral medications with a narrow therapeutic index should be adequately monitored when concomitantly administered.5

CONTRAINDICATIONS
Dulaglutide has an absolute contraindication in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.5 Dulaglutide should also not be used if there is a history of serious hypersensitivity to dulaglutide or any product components.5

WARNINGS AND PRECAUTIONS
Dulaglutide carries a boxed warning of thyroid C-cell tumors and may result in an increased risk for medullary thyroid carcinoma and pancreatitis. If a patient suspects the development of pancreatitis, dulaglutide should be discontinued.5 Dulaglutide is not recommended in patients with severe gastrointestinal (GI) disease (i.e., colitis, Crohn’s disease, GI obstruction, GI perforation, gastroparesis, ileus, inflammatory bowel syndrome, pseudomembranous colitis, ulcerative colitis, and/or undiagnosed GI bleeding).5

As with any antidiabetic treatment, hypoglycemia may occur. If dulaglutide is used with an insulin secretagogue (i.e., sulfonylurea, meglitinide) or insulin, consider lowering the dose of the secretagogue or the insulin to reduce the risk of hypoglycemia.5 Renal function should be monitored in patients with renal impairment reporting severe adverse gastrointestinal reactions.

DOSAGE AND ADMINISTRATION
Dulaglutide should be administered once weekly at any time of the day. It is to be injected subcutaneously in the abdomen, thigh, or upper arm. The starting dose is 0.75 mg subcutaneously once weekly.3 The dose can be increased to 1.5 mg once weekly for additional glycemic control. If a dose is missed, administer it within three days (72 hours) of the missed dose.5

COST
The average wholesale price for a 28-day pack with four injection pens (0.75 mg or 1.5 mg) is approximately $690.11

P&T COMMITTEE CONSIDERATIONS
For the type-2 diabetes patient, 11 drug classes are currently available; however, in the hospital setting it can sometimes be unclear which of these agents should be added to the hospital’s formulary. Among the 11 classes of drugs, incretin-based therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have become fundamental treatment options in treatment guidelines. They both target the therapeutic usefulness of the incretin system in distinct ways, but their ultimate goal is to increase insulin release from the pancreatic beta cells and decrease glucagon secretion from the pancreatic alpha cells, which results in decreased hepatic glucose production, slow gastric emptying, improved satiety, and weight loss. However, this mechanism is more often seen in the GLP-1 receptor agonists. GLP-1 receptor agonists mimic the action of incretin, while DPP-4 inhibitors inhibit the DPP-4 enzyme that inactivates incretin, promoting higher levels of incretin during the postprandial phase.

Since the approval of exenatide and sitagliptin, the use of GLP-1 receptor agonists and DPP-4 inhibitors has been widely incorporated into outpatient settings through treatment guidelines and clinical practice. However, it is important to understand that while these new classes of medications could be safe to use in the inpatient population, the long-term safety profile of their use has yet to be determined.12

Many diabetes associations support the use of insulin as the preferred agent in the hospital setting regardless of a history of diabetes because of the short half-life of circulating insulin and the luxury of intravenous administration. This route allows for rapid dosing adjustments upon assessing a patient’s status.13 When examining the classes side by side, there are currently only a handful of studies investigating the use of GLP-1 agonists in the inpatient setting, while there are many studies that support the use of insulin in hospitalized patients. To date, no major benefits have been demonstrated with the use of GLP-1s in the inpatient setting; and in many GLP-1–treated patients, rescue therapy with insulin was required to achieve and maintain the desired glycemic targets. GLP-1s also have an added risk for gastrointestinal side effects such as nausea, vomiting, and constipation.

When compared to other therapies, insulin has also proven to be safe and effective for glycemic management and to reduce hospital complications.14 While there are indeed many advances in diabetes pharmacotherapy, insulin may remain the preferred blood glucose-lowering agent of choice for inpatient hyperglycemia management simply because of its tolerability, cost, and proven long-term results. It is also important to note that patients typically seen in the hospital setting are often in distress, which requires
an immediate action or dose of medication. Noninsulin therapies often take more time to reach their full effectiveness, and OAMs are not able to adjust to the infrequent changes in glucose levels sufficiently. Therefore, any recommendation against the use of noninsulin therapies due to efficacy concerns is warranted.

CONCLUSION

The GLP-1 class of medications has shown its ability to improve glycemic control while reducing body weight and systolic blood pressure in patients with type-2 diabetes. Dulaglutide is the newest edition to the GLP-1 receptor agonist family for the treatment of type-2 diabetes mellitus in conjunction with adequate diet and exercise. Recent studies have demonstrated that dulaglutide is more effective than other antidiabetic agents by reducing the HbA1c by close to or greater than 1%. It is also the only GLP-1 agonist that has had a successful head-to-head trial showing noninferiority to liraglutide.

Similar to other agents in the class, dulaglutide has demonstrated weight loss of approximately 6 pounds, which has been sustained over at least 26 weeks. However, one of the substantial benefits dulaglutide provides, and one that patients may place quite a bit of value on, is the convenience of once-weekly dosing compared with other agents’ once-daily dosing. While dulaglutide use is not without risks and the adverse effects and contraindications must be considered, it is important to take into careful consideration its long-term safety profile by staying abreast of the current research taking place in regard to major cardiovascular events and the risk of pancreatitis or pancreatic cancer. Therefore, while dulaglutide has both risks and advantages, it is currently proven to be an adequate choice of treatment for patients with type-2 diabetes in the outpatient setting.

REFERENCES