Dulaglutide, olodaterol hydrochloride, and vorapaxar sulfate

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Antidiabetic agent

Dulaglutide (Trulicity –Lilly) is the fourth glucagon-like peptide-1 (GLP-1) receptor agonist approved in the United States, joining exenatide (Byetta) and exenatide extended-release (Bydureon), liraglutide (Victoza), and albiglutide (Tanzeum). These agents augment glucose-dependent insulin secretion, and also decrease glucagon secretion and slow gastric emptying, resulting in lower fasting glucose and reduced postprandial glucose excursions in patients with type 2 diabetes.

Dulaglutide is a fusion protein that consists of two identical, disulfide-linked chains, each containing an *N*-terminal GLP-1 analog sequence covalently linked to the Fc portion of a modified human immunoglobulin G4 heavy chain. The GLP-1 analog portion of dulaglutide is 90% homologous to endogenous human GLP-1. Structural modifications have been made to the GLP-1 part of the molecule to confer resistance to dipeptidyl peptidase 4 (DPP-4) mediated proteolysis.

The GLP-1 agonists are administered subcutaneously; like extended-release exenatide and albiglutide, dulaglutide is administered once a week. Liraglutide is administered once a day, and the Byetta formulation of exenatide is administered twice a day. The specific indication for dulaglutide is the same as for the other agents in this class: an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The effectiveness of dulaglutide was demonstrated in six clinical trials that included more than 3,300 patients with type 2 diabetes. It has been studied as a stand-alone therapy, as well as in combination with other antidiabetic agents, including metformin, a sulfonylurea (e.g., glimepiride), a thiazolidinedione (e.g., pioglitazone), and prandial (mealtime) insulin (e.g., insulin lispro), but not in combination with basal insulin. The use of dulaglutide resulted in a lowering of hemoglobin A1c concentrations and improvement in blood glucose control. In studies in which dulaglutide was compared with sitagliptin (Januvia) and twice-a-day exenatide, the new drug provided greater reductions in A1c and fasting plasma glucose concentrations than the latter agents.

As with the other GLP-1 agonists, dulaglutide is not recommended as first-line therapy for patients who are inadequately controlled with diet and exercise. Metformin is the usual initial treatment of choice in patients with type 2 diabetes who do not have risk factors that would preclude the use of this agent. Many patients with diabetes, however, do not experience adequate glycemic control with the use of metformin alone, and a GLP-1 agonist is among the options available for addition to the regimen.

The limitations of use, warnings, and other risks associated with the use of dulaglutide are generally similar to those for the other GLP-1 agonists. It is not indicated for the treatment of patients with type 1 diabetes or patients with diabetic ketoacidosis. Dulaglutide has not been studied in patients with severe gastrointestinal disease including severe gastroparesis, and its use is not recommended in patients with preexisting severe problems of this type. Acute pancreatitis has been infrequently experienced with the use of the GLP-1 agonists, including dulaglutide, and treatment should be promptly discontinued if pancreatitis is suspected. Dulaglutide was not studied in patients with a history of pancreatitis, and other antidiabetic agents should be considered for use in patients with such a history.

Certain risks associated with dulaglutide therapy are included in a boxed warning. There have been reports of thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in studies of GLP-1 agonists in rodents. Although it is not known whether dulaglutide causes these tumors in humans, its use is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2.

The adverse events most often reported (and their incidence with doses of 0.75 mg and 1.5 mg once a week, respectively) in clinical studies of dulaglutide include nausea (12%; 21%), diarrhea (9%; 13%), vomiting (6%; 13%), abdominal pain (7%; 9%), and decreased appetite (5%; 9%). Severe hypersensitivity reactions have been infrequently experienced and treatment should be discontinued if such a reaction occurs.

Many patients with diabetes are overweight. Some antidiabetic agents such as insulin and the sulfonylureas have been associated with weight gain during treatment. Conversely, many patients treated with a GLP-1 agonist experience weight loss. Although dulaglutide and albiglutide have not been directly compared in clinical studies, the data

The **New Drugs** column informs readers about new chemical and biologic entities approved for marketing by the U.S. Food and Drug Administration. The column is written by Contributing Editor Daniel A. Hussar, PhD, Remington Professor of Pharmacy, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia.

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