Exenatide: From the Gila Monster to the Pharmacy

Curtis Triplitt and Elaine Chiquette

ABSTRACT

Objective: To explain the incretin concept and review the pharmacology and clinical utility of exenatide (Byetta—Amylin; Lilly), a new agent for the treatment of patients with type 2 diabetes mellitus, and provide pharmacists with information necessary for counseling patients in the use of exenatide.

Data Sources: Review articles, clinical trials, and data on file with the manufacturers.

Study Selection: By the authors.

Data Extraction: By the authors.

Data Synthesis: Exenatide is a synthetic form of a protein found in the saliva of the Gila monster that mimics the action of glucagon-like peptide-1, an incretin important in glucose homeostasis and deficient in patients with diabetes mellitus. Three pivotal clinical trials of exenatide as an add-on therapy in patients with type 2 diabetes mellitus who were unable to achieve glycemic control with maximum doses of metformin, sulfonylurea, or these drugs in combination demonstrated significant reductions in glycosylated hemoglobin (A1C) levels following twice-daily self-injection of exenatide compared with placebo. Weight loss was observed in patients in conjunction with A1C improvement, which occurred without additional patient instruction, intentional caloric deficit, or exercise. Mild-to-moderate nausea was the most common adverse event with exenatide treatment, occurring at the beginning of therapy, lessening over time, and reduced by titration of the dose.

Conclusion: Exenatide offers a wide range of beneficial glucoregulatory effects, including enhancement of glucose-dependent insulin secretion, restoration of first-phase insulin response, suppression of inappropriately elevated glucagon secretion, slowing of gastric emptying, and reduction of food intake. These positive effects depend on the patient's understanding of the proper administration technique and timing, the need for continued adherence, and what to do if adverse effects occur, all elements that can be conveyed by pharmacists in their counseling and education of patients with type 2 diabetes mellitus.

Keywords: Exenatide, incretins, diabetes mellitus, glucagon-like peptide-1.

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Diabetes affects an estimated 18.2 million Americans and contributes to almost 200,000 deaths per year. The prevalence of diabetes in the United States increased by 49% between 1990 and 2000.[1] More alarming is that the largest increase (76%) occurred among young adults aged 30 to 39 years. Because the prevalence of obesity is rising in American adults and children, type 2 diabetes mellitus (T2DM) is likely to become even more common.[2] For every kilogram increase in self-reported weight in one study, the estimated risk for diabetes increased by approximately 9%.[3] The dual epidemics of obesity and diabetes require immediate attention. The rapid rise in the incidence of T2DM could, if uncontrolled, lead to a higher incidence of diabetes-related microvascular (e.g., eye, kidney, and nerve disease) and macrovascular (e.g., myocardial infarction, stroke) diseases. Furthermore, both complications (microvascular and macrovascular) can be directly linked to poor glycemic control.[4]

AT A GLANCE

Synopsis: Exenatide (Byetta—Amylin; Lilly) is the first agent in a new class of drugs, the incretin mimetics, for the treatment of patients with type 2 diabetes mellitus. Exenatide is a synthetic form of a protein found in the saliva of the Gila monster, a large lizard that is native to Mexico and the southwestern United States. Exenatide has demonstrated a wide range of glucoregulatory effects in clinical trials. In pivotal trials, exenatide was generally well tolerated and demonstrated significant improvements in glycosylated hemoglobin (A1C) levels in patients with type 2 diabetes mellitus who were unable to achieve glycemic control with maximum doses of metformin, sulfonylurea, or a combination of metformin and sulfonylurea. These positive effects depend on proper use and adherence.

Analysis: *Despite available therapeutic agents, about 60% of the growing number of patients with diabetes do not achieve target A1C levels. In addition, glucose control declines over time even with the use of sulfonylureas or metformin, in part because of the chronic and progressive nature of the disease. Exenatide provides a therapeutic option that allows additional patients to achieve and/or maintain glycemic control, especially patients who are unable to achieve control with maximum doses of metformin or sulfonylurea. The patient's understanding of the proper exenatide administration technique, timing, and need for continued adherence is critical in achieving positive outcomes. Using the tools and information provided in this article, pharmacists should counsel patients who have been prescribed exenatide on these points and ensure that patients have the tools they need for optimum health outcomes.*

Despite the availability of many antidiabetic agents, approximately 60% of individuals with diabetes do not achieve target glycosylated hemoglobin (A1C) levels.[5–7] The difficulty in achieving A1C goals can be explained in part by the chronic and progressive nature of T2DM. The United Kingdom Prospective Diabetes Study (UKPDS) clearly showed that treatment with sulfonylureas or metformin was more effective than dietary therapy alone in producing an initial decline in A1C. However, after about 12 months, A1C began to increase in patients taking oral agents at approximately the same annual rate as in patients treated with diet alone. After 3 years, more than 50% of the patients treated with sulfonylurea or metformin monotherapy had lost glycemic control and, by 6 years of follow-up, more than 50% of all patients required insulin therapy.[8] Once on insulin the patients in the intensive group, which targeted a fasting plasma glucose of less than 108 mg/dL, experienced an average weight gain of 9 pounds and had significantly more episodes of major hypoglycemia compared with the conventional group, whose goal was to achieve glucose levels of less than 270 mg/dL.[9]

In summary, lessons learned from UKPDS are that (1) newly diagnosed patients with T2DM already have lost almost one half of their beta-cell function; (2) despite treatment with diet, metformin, or sulfonylureas, a progressive 4%–5% yearly loss occurs in pancreatic beta-cell function, and (3) sulfonylurea and insulin therapy result in increased weight gain and hypoglycemic episodes.[10]

Clearly, additional therapeutic options are needed, preferably ones that will further improve glycemic control, allow more patients to reach glycemic goals, reduce weight, and overcome other clinical shortcomings of available agents.

Objective

Exenatide (Byetta—Amylin; Lilly) is a new agent for the treatment of patients with T2DM, and is the first drug in a new class known as incretin mimetics. The incretin concept and the pharmacology and clinical utility of exenatide are discussed in this review article. Information to help the pharmacist in counseling and education on the use of exenatide in patients with T2DM is also provided.

Incretin Concept

The incretin effect was first documented in the 1960s during an experiment in which similar elevations in plasma glucose, elicited by administration of glucose either by oral or intravenous routes, resulted in a greater insulin secretory response when glucose was administered through the oral route (Figure 1). This observation suggested that gut-derived factors signaling pancreatic beta cells played an important role in postprandial insulin release. The gut hormones responsible for most of the incretin effect are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic