# $A_{1c}$ Management and Modest Weight Loss in Type 2 Diabetes

According to national statistics, more than 20 million Americans—approximately 7% of the population—have type 2 diabetes.[1] With the number of new cases of type 2 diabetes rising each year in the United States, physicians have been challenged to find new approaches to managing the disease, particularly for patients who do not achieve adequate glucose control with lifestyle changes and oral antidiabetic medications. A recent addition to the list of treatment options for such patients is exenatide (BYETTA®, Amylin and Lilly), which has been on the market since April 2005. This agent, the first and only in a new class of drugs known as incretin mimetics, is an effective option for patients not adequately controlled on oral antidiabetic medications alone.[2]

## Background

For those persons living with type 2 diabetes, a key to avoiding serious medical complications is to maintain adequate glycemic control. The recommended target glycemic level set by the American Diabetes Association is a glycosylated hemoglobin $A_{1c}$ ($HbA_{1c}$) level <7%.[3]

Physicians who treat patients with type 2 diabetes routinely attempt to reach this goal in several steps. The first is advising patients to make necessary dietary and physical activity changes to modify glycemic levels and, if they are overweight, to lose weight. Second, when lifestyle changes fail to achieve and maintain blood glucose levels within the recommended range, an oral blood-glucose-lowering medication is prescribed.[3] Finally, if adequate glucose control is not achieved with one or more oral medications, the addition of insulin replacement therapy is often the next step.[4] The majority (57%) of adults with type 2 diabetes take an oral medication to control their glucose levels, 16% take insulin, and 12% take both insulin and an oral medication.[1]

## An Effective Option

Exenatide, the first and only incretin mimetic medication, is used to improve glucose levels in combination with one or more oral antidiabetic medications—metformin and/or a sulfonylurea; or a thiazolidinedione (with or without metformin). BYETTA mimics several actions of glucagon-like peptide-1 (GLP-1), a naturally occurring incretin hormone that is a fundamental component of normal glucose management. Some of the actions of GLP-1 include its ability to enhance glucose-dependent insulin secretion and delay gastric emptying, both of which reduce hyperglycemia.[5] GLP-1 also enhances ß-cell function, increases satiety, and reduces body weight.[5]

GLP-1 has limitations, however, because it is quickly degraded by dipeptidyl peptidase IV. BYETTA, the only incretin mimetic that can elicit the functions of GLP-1 without its limitations, is gaining increased attention from clinicians who treat patients with type 2 diabetes.

## Clinical Effectiveness

When used as an adjunct to oral therapy, exenatide has been proven to reduce $HbA_{1c}$ levels with weight loss.[6-8]

In one registration study,[6] 233 adults with type 2 diabetes being treated with thiazolidinedione (with or without metformin) were also administered 10 µg of exenatide or placebo twice daily for 16 weeks. The patients receiving exenatide had their $HbA_{1c}$ levels decrease by an average of 0.89% ± 0.09% (± SE). In contrast, patients in the placebo group had increases in $HbA_{1c}$ of 0.09 ± 0.10% (± SE). The investigators found that of the patients who were given the 10-µg dosage of exenatide in addition to their thiazolidinedione (with or without metformin), 62% achieved $HbA_{1c}$ levels ≤7%. By comparison, 16% of the patients in the placebo group, taking only thiazolidinedione with or without metformin, were able to achieve $HbA_{1c}$ levels of ≤7% ($P$<0.001).

In a second registration trial,[8] those taking exenatide for 30 weeks had similar results. Of the patients who received 10 µg of exenatide daily (with metformin), 46% reached $HbA_{1c}$ levels ≤7%. These percentages were significantly greater than the 13% of patients who took metformin only and were able to achieve $HbA_{1c}$ levels ≤7% ($P$<0.0001).

Improvement in glucose control also has been reported with long-term therapy of exenatide of up to 3 years, with $HbA_{1c}$ levels maintained throughout this period.[9]

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## Exenatide Versus Insulin Glargine

Investigators have evaluated the safety and efficacy of adding either exenatide or basal insulin in patients already taking oral medications. For patients who are candidates for either therapy, exenatide's weight loss benefits may be a chief deciding factor.

For example, in a multinational, randomized, open-label, crossover noninferiority study of 138 patients who received either exenatide 10 µg or insulin glargine, Barnett and colleagues[2] found that reductions in $HbA_{1c}$ among those treated with either exenatide or insulin glargine averaged 1.36%. What's more, patients in the exenatide group had significantly lower 2-hour postprandial glucose excursions in the morning, at midday, and in the evening ($P$<0.001).

## Weight Loss

In addition to significant reductions in $HbA_{1c}$ levels, patients taking exenatide benefit from its effect on weight loss.[2,7,8] A unique characteristic of the drug is to slow accelerated gastric emptying and reduce food intake.

Since 85% of patients with type 2 diabetes are overweight, a product that also offers weight reduction in addition to glucose control should be considered. In exenatide trials, in addition to improved glucose control, most patients lost weight.[2,10] For instance, Barnett and colleagues[2] found that patients lost an average of almost 4.5 lbs during exenatide treatment, but gained 2 lbs while on insulin glargine. Two other clinical trials showed that exenatide treatment often led to an average weight loss of 3.3 to 6 lbs over a 30-week period.[7,8] It is important to note that these decreases in body weight were achieved without instruction to modify diet or exercise.

In my practice, I've found that weight loss associated with exenatide therapy is improved if drug treatment is coupled with nutritional counseling. I suggest that my patients visit a dietitian who can reinforce weight loss principles and provide instructions on making more appropriate food selections.

## Adverse Events

Results of numerous studies conclude that exenatide therapy is well tolerated by most patients. The most common complaints are gastrointestinal side effects: nausea or vomiting. Mild-to-moderate nausea is the most frequent adverse event reported with exenatide treatment.[7]

Kendall and colleagues[7] reported that of the 241 patients in a 10-µg treatment group, 117 (48.5%) experienced nausea. The researchers found that nausea was most prevalent in the first weeks of therapy—usually between weeks 0 and 8—but incidence typically declined over time.

Additionally, Barnett and colleagues found that nausea was more common in the patients who were on exenatide compared with those on insulin glargine (42.6% vs 3.1%).[2]

Patients who experience mild symptoms may achieve relief of this side effect by starting the drug at a low dosage and gradually increasing it, as well as by adjusting the time of day the medication is administered. I've found that having my patients take exenatide 15 to 30 minutes before eating may be helpful. However, to benefit from the drug's effect on food intake, I caution my patients that the time between dosing and their meal should not be any closer than 15 minutes. Patients also may find relief from nausea by sucking on a hard candy, such as a lemon drop, a mint, or crystallized ginger.

## Conclusion

Glucose control is one of the main approaches to managing type 2 diabetes and preventing serious sequelae related to this disease. Some patients are able to achieve the $HbA_{1c}$ target level of ≤7% by lifestyle changes and/or using oral medications. For those patients who require additional intervention, exenatide therapy may be considered an appropriate adjunctive therapy to oral antidiabetic drugs. Nausea, the most common side effect of exenatide, is manageable in most patients by starting the drug at a low dosage and gradually increasing it, as well as by adjusting the timing of dosing. Evidence from clinical studies shows that exenatide lowers blood glucose levels, reduces body weight, and is generally well tolerated.

**Nausea is the most common adverse event; for information about hypoglycemia, nausea, and pancreatitis, and other important safety information, please see the Brief Summary of Prescribing Information for BYETTA on the adjacent page.**

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