# Safety of Exenatide Once Weekly in Patients With Type 2 Diabetes Mellitus Treated With a Thiazolidinedione Alone or in Combination With Metformin for 2 Years

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## ABSTRACT

**Background:** Patients with type 2 diabetes mellitus are routinely treated with combinations of glucose-lowering agents. The adverse event (AE) profile and effects on glycemic control have not been assessed for the glucagon-like peptide-1 receptor agonist exenatide once weekly in combination with a thiazolidinedione (TZD) with or without metformin.

**Objective:** This study was conducted to examine the long-term safety profile and changes in glycemic control and weight for exenatide once weekly with TZD with or without metformin in patients with type 2 diabetes mellitus over 2 years.

**Methods:** In this single-arm, open-label trial with treatment up to 104 or 117 weeks, patients received 2 mg exenatide once weekly while continuing treatment with a TZD with or without metformin. Patients were either exenatide-naïve before this study or had previously received exenatide twice daily, which was discontinued on initiating exenatide once weekly. Patients were on a stable dosage of TZD (rosiglitazone or pioglitazone) and, if applicable, metformin. Treatment-emergent AEs were defined as those first occurring or worsening post baseline. Descriptive statistics were used for absolute and change-from-baseline data, and a one-sample *t* test for within-group change in glycosylated hemoglobin ($HbA_{1c}$).

**Results:** Of 134 patients in the intent-to-treat population (baseline mean [SD] $HbA_{1c}$,7.2% [1.0%]), 44 were exenatide-naïve (baseline $HbA_{1c}$, 7.8% [1.0%]) and 90 switched from exenatide twice daily (baseline $HbA_{1c}$, 7.0% [0.8%]). Of intent-to-treat patients, 106 (79%) completed the final treatment visit (week 104 or week 117). The most common AEs were nausea (17% of patients) and injection-site nodule (12% of patients). Serious AEs were reported in 14% of patients and 5% withdrew because of a treatment-emergent AE. No identifiable pattern of serious AEs was observed. There were 4 reports of edema and no reports of heart failure. No major hypoglycemia was reported; minor hypoglycemia was reported in 4% of patients. Exenatide-naïve patients experienced mean (SE) $HbA_{1c}$ reductions of −0.7% (0.2%) and weight reductions of −2.7 (0.8) kg, whereas patients with prior exposure to exenatide twice daily experienced a reduction of −0.4% (0.1%) in $HbA_{1c}$ and no change in weight.

**Conclusions:** Adverse events over 2 years were consistent with the reported safety profiles of exenatide once weekly and TZDs. Exenatide-naïve patients experienced improvements in $HbA_{1c}$ and weight, while patients with the benefit of prior exenatide therapy experienced an additional reduction from baseline in $HbA_{1c}$ and no additional change in weight after 2 years. ClinicalTrials.gov identifier: NCT00753896. (*Clin Ther.* 2012;34:2082–2090) 

**Key words:** exenatide, GLP-1 receptor agonist, metformin, glucose control, $HbA_{1c}$, type 2 diabetes mellitus, TZD.

## INTRODUCTION

Exenatide is a glucagon-like peptide-1 receptor (GLP-1R) agonist that has been approved for the treatment

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of type 2 diabetes mellitus (T2DM) in twice-daily and once-weekly formulations. Exenatide has been shown to work through multiple mechanisms of action, including glucose-dependent enhancement of insulin secretion, inhibition of inappropriately elevated glucagon secretion, slowing of gastric emptying, and reduction of food intake.[1] Exenatide twice daily and exenatide once weekly have been shown to cause reductions in glycosylated hemoglobin ($HbA_{1c}$) and have been associated with reductions in fasting and postprandial glucose concentrations and weight.[2–6] Both agents are generally well tolerated, with gastrointestinal events (for exenatide once weekly and twice daily) and injection-site reactions (for exenatide once weekly) being the most commonly reported adverse events (AEs).[2–7]

Thiazolidinediones (TZDs), which are peroxisome proliferator–activated receptor γ agonists, work through mechanisms of action that are different than, and possibly complementary to, exenatide, in that TZD therapy improves glucose disposal by reducing insulin resistance.[8,9] However, TZD use has been associated with increased weight, fluid retention, heart failure, and, in the case of rosiglitazone, myocardial infarction.[10–15]

Routinely, patients with T2DM are treated with combinations of glucose-lowering agents to achieve blood glucose targets. Current treatment guidelines for T2DM position GLP-1R agonists both directly after metformin and among options for dual and triple combination therapy with metformin or TZD, or both.[16,17] In a previous study of patients with T2DM suboptimally controlled with a TZD (with or without metformin), treatment with exenatide twice daily for 16 weeks resulted in improved glycemic control and weight loss, with AEs consistent with the known safety profile of exenatide.[18] Similar results for glycemic control and safety were observed in a 26-week study and in a post hoc pooled analysis of patients treated with exenatide twice daily and a TZD for 12 to 30 weeks.[19,20] In the present study, we assessed the long-term (104 to 117 weeks) safety profile of an extended-release formulation of exenatide in which exenatide is encapsulated in microspheres, exenatide once weekly, in patients with T2DM treated with a TZD with or without metformin in a single-arm, open-label, multicenter Phase III safety study. Changes from baseline in measures of glycemic control, including $HbA_{1c}$ and fasting serum glucose (FSG), and weight were also assessed. Twenty-six–week interim results have been reported previously.[21]

## METHODS

This trial was conducted in agreement with the Declaration of Helsinki, including all amendments through the Seoul revision and the International Conference on Harmonisation Guideline for Good Clinical Practice.[22] The protocol was approved by local ethical review committees or institutional review boards. All participants gave written informed consent before inclusion in the study.

Patients were recruited from 23 study centers in the United States, Canada, Mexico, Romania, and South Africa. Patients were at least 18 years of age, had an $HbA_{1c}$ level ≤10.0% at screening if previously treated with exenatide twice daily or an $HbA_{1c}$ level of 7.1% to 10.0% at screening, inclusively, if not previously treated with exenatide twice daily; a body mass index of 25 to 45 kg/m$^2$, inclusively; and weight not varying by >10% for at least 3 months before screening. Patients were on a stable TZD dosage (>4 mg/d rosiglitazone or ≥30 mg/d pioglitazone), with or without metformin, for at least 120 days before screening. Patients treated with metformin were on a stable dosage for at least 90 days before screening. Patients were included if they (1) had never received exenatide twice daily, (2) had been treated with commercially available exenatide twice daily for at least 3 months, or (3) completed a previous clinical trial involving exenatide twice daily plus a TZD within 3 months before screening. Patients recruited from a previous clinical trial that assessed the safety and efficacy of exenatide twice daily in combination with a TZD had received either placebo or exenatide twice daily.[18] Exclusion criteria included treatment with medications to promote weight loss within 3 months of screening, previous treatment with other GLP-1 analogs or liraglutide, or treatment with any of the following for 2 weeks or longer within 3 months of screening: insulin, sulfonylureas, α-glucosidase inhibitors, meglitinides, dipeptidyl peptidase-4 inhibitors, or pramlintide acetate.

After screening, patients initiated treatment with exenatide once weekly 2 mg in addition to their ongoing regimen of TZD with or without metformin. Patients treated previously with exenatide twice daily discontinued twice-daily injections upon switching to exenatide once weekly 2-mg treatment.