

New Drug Approvals

Review of the Safety and Efficacy of Exenatide Once Weekly for the Treatment of Type 2 Diabetes Mellitus

Catherine E Murphy

There is an epidemic of diabetes in the US, with the disease affecting an estimated 25 million people.¹ Complications of diabetes contribute to excess morbidity and mortality and include cardiovascular disease, kidney disease, limb amputation, painful neuropathy, and blindness. Estimated total direct and indirect costs attributed to diabetes in the US were \$174 billion in 2007 and are likely more than that now given the increasing prevalence of the disease.² The excess morbidity and mortality and staggering costs attributed to diabetes underline the need for effective prevention and treatment.

Although recent studies have questioned the clinical benefit of aggressive glycemic control, a hemoglobin A_{1c} (A1C) less than 7.0% is an appropriate glycemic goal for most patients.³⁻⁵ This should be targeted with lifestyle modifications and pharmacologic therapies while avoiding severe hypoglycemia and adverse effects. Unfortunately, despite the availability of multiple effective antihyperglycemic therapies, almost half of patients with diabetes continue to have suboptimal glycemic control.⁶

Modest weight loss can improve glycemic control and prevent progression or development of the disease, but most patients require pharmacologic therapy to manage hyperglycemia.^{7,8} Guidelines for treatment of type 2 diabetes recommend metformin as the initial therapy for most patients because of its efficacy, safety, tolerability, and low cost.^{9,10} Al-

OBJECTIVE: To summarize and evaluate the available literature assessing the efficacy and safety of exenatide once weekly for the treatment of type 2 diabetes mellitus.

DATA SOURCES: PubMed (1966-January 2012) and *International Pharmaceutical Abstracts* (1969-January 2012) were searched using the term exenatide once weekly. Abstracts presented at the European Association for the Study of Diabetes Annual Meeting in 2011 and reference citations from publications were reviewed for inclusion. Eli Lilly and Company and Amylin Pharmaceuticals were contacted for additional unpublished information.

STUDY SELECTION AND DATA EXTRACTION: All English-language articles and abstracts were evaluated for inclusion. All randomized controlled trials were included in the review.

DATA SYNTHESIS: The efficacy and safety of exenatide once weekly has been evaluated as initial monotherapy and as add-on therapy to metformin, sulfonylureas, and thiazolidinediones in patients with uncontrolled type 2 diabetes for up to 3 years. Results from 6 randomized, comparator-controlled studies in over 3000 patients indicate that treatment with exenatide once weekly results in significant glycemic improvements and weight loss. Gastrointestinal adverse effects and injection site reactions are common, but rarely lead to drug discontinuation.

CONCLUSIONS: Exenatide once weekly holds promise as a convenient, efficacious, and well-tolerated antihyperglycemic agent for the treatment of type 2 diabetes. Studies evaluating outcomes such as cardiovascular events or all-cause mortality with exenatide once weekly are lacking.

KEY WORDS: bydureon, exenatide extended-release, exenatide once weekly, type 2 diabetes mellitus.

Ann Pharmacother 2012;46:812-21.

Published Online, 5 Jun 2012, *theannals.com*, DOI 10.1345/aph.1Q722

ternatives to metformin monotherapy include thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) agonists. Advantages of GLP-1 agonists include the low incidence of hypoglycemia and associated weight loss; disadvantages include the need for administration via injection, frequent gastrointestinal adverse effects, and cost. Current guidelines do not recommend GLP-1 agonists as a first-line option, but they should be considered as monotherapy or adjunctive

Author information provided at end of text.

therapy when hypoglycemia or weight loss is of particular concern, or when postprandial hyperglycemia is the primary target. These recommendations were published before the approval of liraglutide, a long-acting GLP-1 agonist with a less pronounced effect on postprandial glucose (PPG) than exenatide twice daily.¹¹

The first GLP-1 agonist, exenatide, was approved by the Food and Drug Administration (FDA) in 2005 as a twice-daily subcutaneous injection.¹² Multiple studies have demonstrated that treatment with exenatide twice daily results in reduction of both fasting and postprandial glucose and A1C lowering of up to 1.1% (generally about 0.6-0.9%).¹³⁻¹⁶ Advantages of exenatide twice daily include weight loss of approximately 2-3 kg and a low incidence of hypoglycemia. However, the usefulness of this formulation is limited by the high rate of gastrointestinal adverse effects, most notably nausea and vomiting, and the inconvenience of twice-daily injections that must be administered within 60 minutes before meals. Furthermore, the twice-daily formulation does not result in 24-hour glycemic coverage, and the rapid increase in exenatide serum concentrations after dosing may contribute to the high rate of gastrointestinal adverse effects.

Liraglutide was approved in 2010.¹⁷ The longer half-life (12 hours vs 2.4 hours for exenatide) allows for once-daily dosing, which affords a more convenient administration schedule than exenatide twice daily. Additionally, liraglutide results in greater reductions in fasting plasma glucose (FPG) and an approximately 0.3% greater reduction in A1C than exenatide twice daily.¹¹ Reductions in PPG after breakfast and dinner are greater with exenatide twice daily. Weight loss and overall tolerability with liraglutide appear to be similar to exenatide twice daily, while the incidence of hypoglycemia is significantly lower with the longer acting GLP-1 agonist.¹¹ The incidence of nausea and vomiting with liraglutide is slightly lower than that seen with exenatide twice daily, and gastrointestinal adverse effects tend to be more transient with liraglutide.

The recent development of a once-weekly exenatide formulation may provide a more convenient antihyperglycemic option for many patients with uncontrolled type 2 diabetes. This new formulation uses biodegradable microsphere technology to encapsulate the active drug and slowly release exenatide into the systemic circulation after subcutaneous injection. The result is therapeutic drug concentrations over the entire dosing interval and a more gradual increase in serum drug concentrations after dosing, leading to the potential for greater efficacy and improved gastrointestinal tolerability. Exenatide extended-release was approved in January 2012 as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes. This article reviews and evaluates the evidence for the use of exenatide once weekly in the treatment of type 2 diabetes and its potential place in therapy.

Data Sources

A literature search was performed to identify English-language articles and abstracts using the search term exenatide once weekly. Databases searched consisted of PubMed (1966-January 2012) and *International Pharmaceutical Abstracts* (1969-January 2012). Abstracts presented at the European Association for the Study of Diabetes Annual Meeting in 2011 were also reviewed for relevance and inclusion. Eli Lilly and Company and Amylin Pharmaceuticals, the developers of exenatide once weekly, were contacted for any available unpublished information and reference citations from recent publications were reviewed. All randomized controlled trials evaluating the efficacy and/or safety of exenatide once weekly were selected for review.

Mechanism of Action

GLP-1 is an incretin hormone secreted by enteroendocrine cells in the intestinal mucosa in response to nutrient intake. The peptide has multiple glucoregulatory actions, including enhancement of glucose-dependent insulin secretion, suppression of glucagon secretion, inhibition of gastric emptying, and reduction in food intake.¹⁸ Exenatide is a GLP-1 receptor agonist with an amino acid sequence similar to that of human GLP-1.¹² Exenatide binds to and activates GLP-1 receptors, resulting in pharmacologic actions similar to those of GLP-1 in the body and a reduction in both FPG and PPG concentrations.

Pharmacokinetics

Exenatide once weekly incorporates a technology with biodegradable polymer-based microspheres that encapsulate the active drug.¹⁹ When the formulation is injected subcutaneously, the microspheres degrade slowly, allowing gradual, controlled release of the drug into the systemic circulation.

The pharmacokinetics of exenatide once weekly have been assessed in 1 single-dose and 2 multiple-dose studies in patients with type 2 diabetes.²⁰⁻²² Exenatide once weekly demonstrated a multiphasic concentration-time profile, with a small initial release of exenatide leading to an initial time to maximum concentration of 2.1-5.1 hours after a single dose, and 2 subsequent phases of drug release several weeks later, resulting in an overall mean time to maximum concentration of 6-7 weeks.²² Administration of exenatide 2 mg once weekly resulted in minimal therapeutic concentrations (>50 pg/mL) in approximately 2 weeks and steady-state concentrations of approximately 300 pg/mL within 6-7 weeks.²² Steady-state concentrations achieved with exenatide 2 mg once weekly are similar to the maximum concentration attained after a single dose of immediate-release exenatide 10 µg.²² The median half-life of exenatide once weekly is approximately 2 weeks. After discontinuation, concentrations decrease to less than 50 pg/mL in approximately 6-7 weeks.

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and fall below the minimal detectable concentration (10 pg/mL) within approximately 10 weeks. Other pharmacokinetic data for exenatide once weekly would not be expected to differ from the twice-daily formulation. Exenatide twice daily is predominantly eliminated via glomerular filtration and has a mean apparent clearance of 9.1 L/h.¹² Mean apparent volume of distribution is 28.3 L.

Clinical Efficacy

The clinical development of exenatide once weekly consisted of 6 pivotal Phase 3 studies comprising the DURATION program (Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly). The DURATION studies evaluated the efficacy and safety of exenatide 2 mg once weekly in patients with uncontrolled type 2 diabetes compared to exenatide twice daily or other antihyperglycemics (Table 1).^{21,23-27} All of the studies were sponsored by Eli Lilly and Amylin Pharmaceuticals, and study sponsors were involved in the design, protocol development, collection, review, interpretation, and analysis of data, as well as preparation of the study manuscripts.

Background therapy in the DURATION studies consisted of diet and exercise alone, or 1 or more oral antihyperglycemics (metformin, a sulfonylurea, or pioglitazone). Inclusion criteria included baseline A1C of 7.1-11.0%, stable body weight, and body mass index (BMI) of 25-45 kg/m². Exclusion criteria varied depending on the study. The primary efficacy end point for each study was change in A1C from baseline to the end of the study; secondary end points included proportion of patients achieving a target A1C (<7.0% or <6.5%), change in FPG, and change in body weight. Each

study also reported the incidence of treatment-emergent adverse events and changes in blood pressure and lipid levels. None of the DURATION studies reported or were powered to compare differences in clinical outcomes such as cardiovascular events or all-cause mortality. Baseline characteristics of patients included in the DURATION clinical trial program were similar among the studies and included mean A1C 8.3-8.6%, FPG 164-178 mg/dL, and BMI 31-35 kg/m². Individual results of each DURATION study are summarized below and in Table 2.^{21,23-27}

EXENATIDE ONCE WEEKLY COMPARED TO EXENATIDE TWICE DAILY

DURATION-1²¹ and DURATION-5²³ were randomized, controlled, open-label, noninferiority studies that compared the efficacy and safety of exenatide once weekly to that of exenatide 10 µg twice daily as initial monotherapy or add-on therapy over 24-30 weeks. Participants were being treated with diet and exercise alone or background oral antihyperglycemic therapy with up to 2 medications (any combination of metformin, a sulfonylurea, and/or a thiazolidinedione). Although both are described as noninferiority studies, superiority analyses were conducted for all outcomes. All safety analyses were reported for the intent-to-treat (ITT) population. Although most efficacy results were reported for the ITT population, DURATION-1 reported some secondary glycemic end points only for the modified per-protocol population (defined as participants who completed study procedures until no more than 4 weeks remained until the end of the study).

Results of DURATION-1 demonstrated significantly greater reductions in A1C and a significantly greater propor-

Table 1. Summary of Pivotal Studies

Study	Comparator	Design	Duration	Pts, N	Background Treatment
DURATION 1 ²¹	Exenatide 10 µg twice daily	Randomized, open-label, non-inferiority, comparator-controlled	30 weeks (plus open-ended extension phase)	295	Diet and exercise, metformin, sulfonylurea, thiazolidinedione, or combination of 2
DURATION 2 ²⁴	Sitagliptin 100 mg once daily, pioglitazone 45 mg once daily	Randomized, double-blind, double-dummy, comparator-controlled	26 weeks (+ 26-week extension phase)	491	Metformin
DURATION 3 ²⁶	Insulin glargine	Randomized, open-label, comparator-controlled	26 weeks (+ 58-week extension phase)	456	Metformin ± sulfonylurea
DURATION 4 ²⁵	Metformin up to 2500 mg once daily, sitagliptin 100 mg once daily, pioglitazone 45 mg once daily	Randomized, double-blind, double-dummy, comparator-controlled	26 weeks	820	Diet and exercise
DURATION 5 ²³	Exenatide 10 µg twice daily	Randomized, open-label, noninferiority, comparator-controlled	24 weeks	252	Diet and exercise, metformin, sulfonylurea, thiazolidinedione, or combination of 2
DURATION 6 ²⁷	Liraglutide 1.8 mg once daily	Randomized, open-label, comparator-controlled	26 weeks	911	Metformin, sulfonylurea, sulfonylurea ± sulfonylurea /thiazolidinedione

tion of patients achieving an A1C goal of less than 7% at the study's end with exenatide once weekly compared to exenatide twice daily.²¹ The proportion of patients achieving the A1C goal was reported only for the modified per-protocol population, thereby likely overestimating the real-world effectiveness of exenatide for this outcome. Treatment with exenatide once weekly resulted in significantly greater improvements in FPG (−41 vs −25 mg/dL; $p < 0.0001$), while improvements in PPG were greater with the twice-daily formulation (−124 vs −95 mg/dL; $p = 0.0124$). Reductions in body weight were similar in both treatment groups.

Consistent with results from DURATION-1, DURATION-5 also demonstrated significantly greater reductions in A1C and FPG (−35 vs −12 mg/dL; $p = 0.0008$) and a greater proportion of patients achieving A1C goal with exenatide once weekly compared to exenatide twice daily.²³ DURATION-5 did not report results for PPG. Weight loss was similar between the study groups, although numerically less than that observed in DURATION-1. This is likely a result of the shorter duration of treatment with the study drug in DURATION-5.

Strengths of both DURATION-1 and DURATION-5 included high completion rates (>80%), few patients lost to follow-up, and the randomized controlled design. Concealment of allocation was described in DURATION-5, but not in DURATION-1. A major weakness of both studies was the unblinded open-label design.

COMPARED TO ORAL ANTIHYPERGLYCEMICS

DURATION-2 was a 26-week randomized, double-blind, double-dummy study that compared the safety, efficacy, and tolerability of exenatide once weekly, sitagliptin 100 mg daily, and pioglitazone 45 mg daily in 491 patients with type 2 diabetes inadequately controlled with metformin monotherapy.²⁴ All results were reported for the ITT population. Exenatide once weekly added to metformin resulted in significantly greater reductions in A1C at 26 weeks compared to sitagliptin or pioglitazone. Reductions in FPG with exenatide once weekly (−32 mg/dL) were significantly greater than those achieved with sitagliptin (−16 mg/dL; $p = 0.0038$ vs exenatide) but not pioglitazone (−27 mg/dL; $p = 0.3729$ vs exenatide).

Table 2. Results from Pivotal Studies

Study	Treatment	Proportion Achieving A1C <7%	Changes							
			A1C, %	Weight, kg	TC, %	LDL-C, %	HDL-C, %	TG, %	SBP, mm Hg	DBP, mm Hg
DURATION 1 ²¹	Exenatide once weekly	77	−1.9 ^a	−3.7 ^a	−7 ^a	−5 ^a	−2	−15	−4.7 ^a	−1.7 ^a
	Exenatide twice daily	61 ^b	−1.5 ^{a,b}	−3.6 ^a	−2	+1	−3 ^a	−11	−3.4	−1.7 ^a
DURATION 2 ^{24,c}	Exenatide once weekly		−1.5 ^a	−2.3 ^a						
	Sitagliptin		−0.9 ^{a,b}	−0.8 ^{a,b}						
	Pioglitazone		−1.2 ^{a,b}	+2.8 ^{a,b}						
DURATION 3 ²⁶	Exenatide once weekly	60	−1.5 ^a	−2.6 ^a	−2 ^a	−2	0	−4	−3 ^a	−1
	Insulin glargine	48 ^b	−1.3 ^{a,b}	+1.4 ^{a,b}	−1	+1	+1	−11	−1	−1
DURATION 4 ²⁵	Exenatide once weekly	63	−1.5 ^a	−2.0					−1.3	
	Metformin	55	−1.5 ^a	−2.0						
	Sitagliptin	43 ^b	−1.2 ^{a,b}	−0.8 ^b					−1.8	
	Pioglitazone	61	−1.6 ^a	+1.5 ^b					−1.7	−2.5
DURATION 5 ²³	Exenatide once weekly	58	−1.6 ^a	−2.3 ^a	−8 ^a	−6 ^a	0	−6	−2.9 ^a	+0.2
	Exenatide twice daily	30 ^b	−0.9 ^{a,b}	−1.4 ^a	0 ^b	+2 ^b	+3	−1	−1.2	−0.1
DURATION 6 ²⁷	Exenatide once weekly	52	−1.3 ^a	−2.7 ^a					−2.5	−0.5
	Liraglutide	60 ^b	−1.5 ^{a,b}	−3.6 ^{a,b}					−3.5	−0.5

A1C = hemoglobin A_{1c}; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides.

^a $p < 0.05$ versus baseline.

^b $p < 0.05$ versus exenatide once weekly.

^cAlthough DURATION-2 evaluated the effects of the study drugs on lipids and blood pressure, numeric values were not reported in the article.

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natide). Weight loss at 26 weeks was also significantly greater with exenatide once weekly compared to sitagliptin and pioglitazone. A methodologic strength of DURATION-2 was its double-blind, double-dummy design. In addition, treatment allocation was concealed and performed via a central site.

DURATION-4 was a randomized, controlled, double-blind 26-week study that compared the efficacy and safety of exenatide once weekly, metformin 2500 mg/day, pioglitazone 45 mg/day, or sitagliptin 100 mg/day as initial monotherapy in 820 patients with uncontrolled type 2 diabetes.²⁵ All results were reported for the ITT population. Treatment with exenatide once weekly resulted in a similar approximate 1.5% reduction in A1C compared to metformin or pioglitazone and a significantly greater reduction than that achieved with sitagliptin. Reductions in FPG with exenatide once weekly (−40.5 mg/dL) were similar to those with metformin (−35.7 mg/dL) and pioglitazone (−46.3 mg/dL) and significantly greater than that with sitagliptin (−20.4 mg/dL; $p < 0.001$). A similar proportion of patients in each treatment group achieved an A1C less than 7.0%, with the exception of sitagliptin, which was less effective with regard to this end point. Both exenatide once weekly and metformin resulted in a similar mean weight loss of 2 kg. Treatment with pioglitazone resulted in weight gain, consistent with previous studies. Strengths of DURATION-4 included the randomized, double-blind study design, concealment of allocation via a central site, and high completion rates (approximately 85%).

COMPARED TO INSULIN GLARGINE

DURATION-3 was an open-label, randomized, 26-week study comparing exenatide once weekly with insulin glargine in 456 patients with type 2 diabetes suboptimally controlled with metformin monotherapy or metformin and sulfonylurea combination therapy.²⁶ Patients were randomized to receive exenatide once weekly or insulin glargine added to their background therapy. Insulin glargine was initiated at 10 units daily and titrated up according to FPG. Analyses were done for the ITT population. Reduction in A1C at 26 weeks was, on average, 0.2% greater for patients receiving exenatide once weekly compared to those receiving insulin glargine ($p < 0.05$). Mean weight loss at week 26 with exenatide once weekly was similar to that in previously described studies, while insulin glargine was associated with weight gain. Reductions in FPG were greater with insulin glargine (−50 vs −38 mg/dL; $p = 0.001$), while reductions in PPG after morning and evening meals were greater with exenatide once weekly (numeric results not reported; $p < 0.05$). The primary methodologic weakness of DURATION-3 was its unblinded, open-label design. Loss to follow-up was very low, and over 90% of patients randomized to treatment completed the study. However, more patients receiving exenatide once weekly withdrew (10.3% vs

6.3%). Although patients and investigators were asked to adhere to titration targets with insulin glargine, no assessment or enforcement of such titration was done. Of note, sulfonylurea background therapy was being used by approximately 30% of patients in each treatment arm. Continuation of a sulfonylurea with initiation of basal insulin may be somewhat controversial due to the potential for additive weight gain with the combination and possible minimal additional glycemic benefit. Consensus guidelines from the American Diabetes Association do not recommend the combination of any insulin with a sulfonylurea.¹⁰ However, the combination of basal insulin and a sulfonylurea is not inconsistent with guidelines from the American Association of Clinical Endocrinologists, whose algorithm for glycemic control specifies that insulin secretagogues must be discontinued on initiation of prandial insulin, but not basal insulin alone.⁹ The guidelines do, however, acknowledge the additive risk of weight gain and fluid retention with the combination, and certainly this likely contributed to the weight gain in the insulin glargine arm in DURATION-3.

COMPARED TO LIRAGLUTIDE

DURATION-6 was a 26-week, open-label, randomized, noninferiority study comparing exenatide once weekly to liraglutide 1.8 mg daily as add-on therapy to metformin, a sulfonylurea, and/or pioglitazone in 911 patients with uncontrolled type 2 diabetes.²⁷ Preliminary results indicated that A1C reduction was 0.2% greater in patients taking liraglutide than exenatide and did not meet the prespecified noninferiority criteria. Liraglutide-treated patients lost significantly more weight and a greater proportion achieved an A1C less than 7%. Of note, the reductions in A1C with exenatide once weekly in this study were of lower magnitude than those seen in the previous DURATION studies, and full results of this study have yet to be published in a peer-reviewed journal and so should be interpreted with caution. A detailed description of study methods is not available and therefore cannot be assessed for validity.

Long-Term Efficacy

Continuation phase results for up to 2 years for DURATION-1, DURATION-2, and DURATION-3 have been published.²⁸⁻³² Analyses of these continuation phase data indicate that improvements in glycemic parameters and weight loss are maintained over the long term. At 2 years, mean change from baseline in A1C was −1.7% and in FPG −40.1 mg/dL; 60% of patients maintained an A1C less than 7%.²⁹ Although a small increase in weight was observed after 26 weeks, weight loss was maintained and at 2 years was approximately a 2-kg reduction from baseline. Results from 3-year data are preliminary, but suggest that improvements in glycemic control and weight loss are maintained at this timepoint.³¹

Effects on Cardiovascular Parameters

None of the DURATION studies assessed the effect of exenatide on cardiovascular morbidity or mortality. Various surrogate cardiovascular markers have been assessed. Although several studies reported a small but significant increase in mean heart rate of about 4 beats/min,^{23,26} most other cardiovascular measures either improved or remained stable during treatment with exenatide once weekly. Improvements, although of questionable clinical significance, were noted in systolic blood pressure (~3-mm Hg reduction) in several studies. At 2 years, blood pressure effects were attenuated, but still improved from baseline.³⁰

Mean total cholesterol and low-density lipoprotein cholesterol levels and triglycerides significantly decreased with exenatide once-weekly treatment, although reductions were small and likely of little clinical significance. Effects on high-density lipoprotein cholesterol were not consistent, with some studies showing a slight decrease²¹ and others finding a significant increase.^{24,25,30} Several studies noted significant ($p < 0.05$) improvements from baseline in other cardiovascular markers as well, including C-reactive protein,²⁴⁻²⁶ adiponectin,²⁴ and B-type natriuretic peptide.²⁴

Preliminary results of analyses from 148 patients in DURATION-1 found no clinically significant effect of exenatide once weekly on QTc interval over 30 weeks of treatment, including in patients with renal dysfunction.³³ Any changes observed in QTc interval were not accentuated in patients with the highest exenatide concentrations.

Adverse Effects

The safety and tolerability of treatment with exenatide once weekly for up to 2 years have been reported. Table 3^{21,23-27} summarizes the most common treatment-emergent adverse events reported in each DURATION study. The overall withdrawal rate resulting from adverse events in patients taking exenatide once weekly was low (4.9%) and most commonly due to nausea.¹² Of note however, withdrawal rates associated with adverse events and overall withdrawal rates were numerically higher with exenatide once weekly than with the comparator drug in several studies (Table 3). The most common adverse effects reported in clinical studies with exenatide once weekly were gastrointestinal (most frequently nausea) and injection site reactions, most commonly injection site nodules. Generally, gastrointestinal adverse effects reported were described as mild to moderate and improved with duration of therapy. Pooled analyses of completed trials (DURATION-1, -2, -3, and -5) found an overall incidence of nausea of 9% with exenatide once-weekly monotherapy, with higher rates in patients on concomitant metformin therapy.³⁴ Discontinuation rates associated with nausea were very low. Gastrointestinal adverse effects were more common with exenatide twice daily than

with exenatide once weekly, while injection site reactions tended to be more common with the once-weekly formulation.

There was one reported case of major hypoglycemia (defined as blood glucose <54 mg/dL associated with loss of consciousness or requiring third-party assistance) with exenatide once weekly.²⁶ This occurred in a patient taking metformin and exenatide once weekly, was not associated with loss of consciousness, and resolved with oral carbohydrate administration. The incidence of minor hypoglycemia was generally low, occurring in about 7% of patients taking exenatide once-weekly monotherapy.³⁴ The highest incidence of hypoglycemia occurred in patients taking a concomitant sulfonylurea.

Drug Interactions

The potential for drug interactions with exenatide once weekly has not been evaluated extensively. Exenatide twice daily has the potential to reduce the extent and rate of absorption of other drugs because of its effect on slowing gastric emptying, and exenatide once weekly would not be expected to differ in this regard.¹² There is limited evidence that the long-acting formulation may have less inhibitory effect on gastric emptying than exenatide twice daily.²¹ The potential for drug interactions may be of particular concern with orally administered medications that have a narrow therapeutic index and/or are dependent on threshold concentrations for efficacy.

Patients taking concomitant antihyperglycemic therapy, particularly sulfonylureas, are at increased risk for hypoglycemia with exenatide once weekly. Reduction of the sulfonylurea dose on initiation of exenatide once weekly should be considered.¹²

Precautions and Contraindications

Exenatide once weekly is contraindicated in patients with a personal or family history of medullary thyroid carcinoma, due to an increased incidence of thyroid cell tumors seen in animal studies. Exenatide once weekly should be avoided in patients with severe renal impairment and should be used with caution in patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min) because of the potential for drug accumulation and worsened renal function from hypovolemia due to drug-induced nausea and vomiting.¹²

Exenatide is not recommended in patients with severe gastrointestinal disease or gastroparesis. Exenatide has been associated with acute pancreatitis, including fatal cases,^{35,36} and should generally be avoided in patients with a history of pancreatitis. There have been 2 cases of pancreatitis reported in clinical studies with exenatide once weekly, both of which resolved.^{23,26}

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Dosage and Administration

Exenatide once weekly is given as a 2-mg subcutaneous injection every 7 days. Unlike the twice-daily formulation, the dose of exenatide once weekly does not require titration and can be administered without regard to meals.

Discussion

Results of the DURATION studies demonstrate significant and consistent improvements in glycemic control with exenatide once weekly, regardless of background antihyperglycemic therapy. A1C reductions were generally about 1.5% after 6 months of treatment. In comparative studies, A1C reductions with exenatide once weekly were greater than those achieved with exenatide twice daily, sitagliptin, or insulin glargine, and were comparable to those of metformin and pioglitazone. Only liraglutide demonstrated significantly greater A1C reduction. Results from as long as 3 years of treatment indicate that improvements in glycemic control are generally sustained, with some modest attenuation over the longer term.^{28,29,31,32}

Although the low discontinuation rates associated with adverse events in clinical studies with exenatide once

weekly suggest reasonable tolerability, withdrawal rates were higher with exenatide once weekly than with the comparator in several studies. Gastrointestinal adverse effects such as nausea and vomiting and injection site reactions were common, although these adverse effects appeared to diminish over time. An advantage of incretin-based agents such as exenatide is the low rate of hypoglycemia, and this was confirmed in the DURATION studies. Hypoglycemia that occurred was predominantly minor, and the majority of cases occurred in patients taking background sulfonylurea therapy. Given the low rate of hypoglycemia with exenatide once weekly, this agent may be preferred over insulin or sulfonylureas in patients for whom hypoglycemia is of particular concern, such as those with inconsistent eating habits or with hypoglycemic unawareness.

Many patients with type 2 diabetes are significantly overweight, a factor that can contribute to insulin resistance and have adverse consequences on other health conditions and general quality of life. A therapeutic advantage of GLP-1 agonists is the beneficial side effect of weight loss. Weight loss in clinical studies with exenatide once weekly was approximately 2-3 kg, similar to that achieved with exenatide twice daily or metformin. Although weight loss tended to be greater in patients with nausea, weight

Table 3. Treatment-Emergent Adverse Events and Withdrawal Rates

Study	Treatment	Adverse Event, %						Withdrawal Rate, %	
		Nausea	Vomiting	Diarrhea	Injection Site Reactions	URI	Hypoglycemia (minor)	Due to Adverse Events	Overall
DURATION 1 ²¹	Exenatide once weekly	26.4	10.8	13.5	22.3	8.1	5.4	6.1	13.5
	Exenatide twice daily	34.5	18.6	13.1	11.7	17.2	6.2	4.8	11.6
DURATION 2 ²⁴	Exenatide once weekly	24	11	18	10	7	1	6.3	25.3
	Sitagliptin	10	2	10	7	16	3	3.0	16.3
	Pioglitazone	5	3	13	7	20	1	3.6	23.8
DURATION 3 ²⁶	Exenatide once weekly	13	4	9	13		8	5	10.3
	Insulin glargine	1	1	4	2		26	1	6.3
DURATION 4 ²⁵	Exenatide once weekly	11.3	4.8	10.9	10.5	7.7	5.2	2.4	15.3
	Metformin	6.9	3.3	12.6	10.2	4.5	4.1	2.4	13.4
	Sitagliptin	3.7	1.8	5.5	6.7	9.8	3.1	0.6	14.1
	Pioglitazone	4.3	3.1	3.7	3.7	8.6	3.7	3.1	18.4
DURATION 5 ²³	Exenatide once weekly	14	4.7	9.3	13	7	3.9	5	15.5
	Exenatide twice daily	35	8.9	4.1	10	4.1	3.3	5	22.8
DURATION 6 ²⁷	Exenatide once weekly	9.3	3.7	6.1	10		10.8	2.6	
	Liraglutide	20.4	10.7	13.1	1		8.9	5.3	

URI = upper respiratory infection.

loss also occurred in those without gastrointestinal adverse effects. In patients for whom weight gain is of particular concern, exenatide once weekly may be preferred over agents such as insulin, thiazolidinediones, or sulfonylureas that can contribute to weight gain.

There are no data on clinical outcomes such as cardiovascular event rates or all-cause mortality with exenatide once weekly. All outcomes assessed in the DURATION studies were surrogate end points, and given the fact that these end points may not correlate with clinical outcomes (case in point, the highly publicized analysis finding adverse cardiovascular effects of rosiglitazone, despite its glycemic benefits³⁷), results should be weighed with caution. However, it is reassuring that effects on lipids and blood pressure were generally positive with exenatide once weekly, with the exception of a small but significant increase in heart rate reported in some studies. Both exenatide twice daily and liraglutide have been associated with increased heart rate as well.^{11,38,39} Although prospective, controlled clinical studies evaluating cardiovascular outcomes are lacking for both exenatide formulations, retrospective analyses indicate that exenatide twice daily does not increase the risk for cardiovascular events and may be associated with lower rates of events.^{40,41} EXSCEL (Exenatide Study of Cardiovascular Event Lowering) is ongoing and will evaluate the effects of exenatide once weekly on major cardiovascular events.⁴²

With its approval, exenatide once weekly has joined exenatide twice daily and liraglutide in the GLP-1 agonist armamentarium available to clinicians. Given their adverse effect profile, as a class, these agents may be preferred in patients for whom hypoglycemia or weight loss is of particular concern. With regard to differences among the GLP-1 agonists, results of comparative studies indicate that liraglutide is the most effective agent for overall glycemic improvement.^{11,27} A1C reduction with liraglutide is approximately 0.3% greater than that achieved with exenatide twice daily and approximately 0.2% greater than with exenatide once weekly. When postprandial hyperglycemia is the primary target, exenatide twice daily has the greatest potential for improvements after morning and evening meals.^{11,21} The longer-acting GLP-1 agonists tend to have greater effects on fasting glycemia than short-acting exenatide does.^{11,21,23}

Withdrawal rates associated with adverse events of all GLP-1 agonists are low. The rate with exenatide once weekly in comparative studies with exenatide twice daily was similar or numerically higher, indicating that the long-acting formulation does not improve overall tolerability.^{21,23} However, both liraglutide and exenatide once weekly demonstrate lower rates of nausea and vomiting than exenatide twice daily.^{11,21,23} Gastrointestinal adverse effects are also less frequent with exenatide once weekly compared to liraglutide, occurring at about half the rate.²⁷ The improved gastrointestinal tolerability with exenatide once weekly is likely due to the release

mechanism of the formulation, which results in slow, gradual increases in concentration as opposed to the more pronounced peaks in concentration after exenatide twice-daily dosing.²² Injection site reactions occurred more frequently with exenatide once weekly in comparative studies with liraglutide and exenatide twice daily, likely because of the mechanism of the formulation.^{21,23,27} All GLP-1 agonists are associated with low rates of hypoglycemia. While liraglutide has demonstrated a significantly lower rate of hypoglycemia than exenatide twice daily,¹¹ exenatide once weekly has not consistently demonstrated a lower rate compared to the twice-daily formulation.^{21,23} Lastly, with regard to weight loss differences, although all 3 agents are associated with significant weight loss, liraglutide has demonstrated greater weight loss potential than exenatide once weekly.²⁷

Unless morning or evening postprandial glycemic excursions are the primary target, the glycemic efficacy, dosing convenience, and improved gastrointestinal tolerability of liraglutide and exenatide once weekly should make both of these agents preferred choices over exenatide twice daily for most patients. The choice between exenatide once weekly and liraglutide will be a matter of weighing the improved overall tolerance and dosing convenience of exenatide once weekly with the potential for greater weight loss and glycemic efficacy with liraglutide.

Summary

Results of the DURATION studies indicate that exenatide once weekly is efficacious, results in significant weight loss, and has a low rate of hypoglycemia. Although the twice-daily formulation has been available for several years and has demonstrated glycemic and weight loss efficacy, the inconvenience of multiple daily injections timed before meals and the high incidence of gastrointestinal adverse effects limit its usefulness. The convenience of once-weekly injections, improved overall glycemic efficacy, and lower rate of gastrointestinal adverse effects with exenatide once weekly will likely make this agent a preferred antihyperglycemic option over its twice-daily counterpart. As with other GLP-1 agonists, exenatide once weekly may be a more preferred antihyperglycemic option in patients for whom hypoglycemia and weight loss or avoidance of weight gain are of particular concern. However, until long-term safety, efficacy, and clinical outcomes are further assessed, exenatide once weekly will likely join other GLP-1 agonists as a second- or third-line option behind more established, low-cost therapies, such as metformin and sulfonylureas.

Catherine E Murphy PharmD BCPS BCACP, Assistant Professor, Albany College of Pharmacy & Health Sciences, Colchester, VT
Correspondence: Dr. Murphy, katie.murphy@acphs.edu
Reprints/Online Access: www.theannals.com/cgi/reprint/aph.1Q722

Conflict of interest: Author reported none

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EXTRACTO

Revisión de la Seguridad y Eficacia de Exenatida Una Vez en Semana Para el Tratamiento de Diabetes Mellitus Tipo 2

CE Murphy

Ann Pharmacother 2012;46:812-21.

OBJETIVO: Resumir y evaluar la literatura disponible que estudió la eficacia y seguridad de exenatida una vez en semana (QW) para el tratamiento de diabetes mellitus tipo 2.

FUENTES DE DATOS: Se realizó una búsqueda de la literatura en los sistemas de datos PubMed (1966- enero, 2012) e *Abstractos Farmacéuticos Internacionales* (1969-enero 2012) utilizando el siguiente término, exenatida una vez en semana. También se revisaron para inclusión los resúmenes de trabajos presentados en la Reunión Anual del 2011 de la Asociación Europea de Estudio en Diabetes y las referencias utilizadas en las publicaciones. Para obtener información adicional, que no estuviera publicada, se contactó a las compañías Eli Lilly y Amilyn Pharmaceuticals.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se evaluaron para inclusión todos los artículos y resúmenes publicados en el idioma inglés. Todos los estudios clínicos, aleatorios, y controlados fueron incluidos en la revisión.

SÍNTESIS DE LOS DATOS: La eficacia y seguridad de exenatida QW se ha evaluado como monoterapia inicial y como tratamiento añadido a metformin, sulfonilureas, y tiazolidinedionas en pacientes con diabetes no controlada por hasta 3 años. Los resultados de 6 estudios aleatorios, controlados con un comparador, en sobre 3000 pacientes indican que el tratamiento con exenatida QW resulta en mejoras significativas en el control glucémico y en pérdida de peso. Los efectos secundarios gastrointestinales y las reacciones en el lugar de inyección fueron comunes pero raramente llevaron al paciente a descontinuar el tratamiento con exenatida.

CONCLUSIONES: Exenatida QW promete ser un agente antihiper glucémico que es conveniente, eficaz, y bien tolerado para ser utilizado en el tratamiento de pacientes con diabetes mellitus tipo 2. No hay estudios que evalúen los resultados en eventos cardiovasculares o mortalidad en general con exenatida una vez en semana.

Traducido por Mirza Martinez

RÉSUMÉ

Revue de l'Efficacité et de l'Innocuité d'Une Administration Hebdomadaire d'Exénatide pour le Traitement du Diabète Type 2

CE Murphy

Ann Pharmacother 2012;46:812-21.

OBJECTIF: Résumer et évaluer la littérature médicale disponible décrivant l'efficacité et l'innocuité d'une administration hebdomadaire (AH) d'exénatide pour le traitement du diabète de type 2.

PROVENANCE DES DONNÉES: Les banques de données PUBMED (1966-janvier 2012) et *International Pharmaceutique Résumé* (1969-janvier 2012) ont été interrogées en utilisant le terme exénatide une fois par semaine. Les résumés des communications présentées à la réunion annuelle de 2011 de l'Association Européenne pour l'Étude du Diabète ont aussi été revus. De plus, les compagnies Eli Lilly et Amylin Pharmaceuticals ont contactées afin d'identifier les données non encore publiées.

SÉLECTION DES DONNÉES: Toutes les publications et résumés de langue anglaise ont été évalués pour inclusion. Les essais comparatifs à répartition aléatoire ont été retenus pour cette revue.

RÉSUMÉ: L'efficacité et l'innocuité de l'exénatide AH ont été évaluées alors que celui-ci était administré en monothérapie initiale ou en thérapie adjuvante (chez les patients dont le diabète type 2 était mal maîtrisé avec les thérapies usuelles tel que la metformine, les sulfonylurés, et les thiazolidinediones). La durée de traitement pouvait atteindre 3 ans dans certaines études. Les résultats de 6 essais comparatifs à répartition aléatoire (versus un traitement de référence) chez plus de 3000 patients indiquent que l'exénatide AH permet une amélioration significative de la glycémie et une perte de poids. Les effets indésirables les plus communs incluent les troubles digestifs et les réactions au site d'injection n'entraînant l'arrêt du traitement qu'en de rares occasions.

CONCLUSION: L'exénatide AH semble une alternative pratique, efficace, et bien tolérée pour le traitement du diabète type 2. Les études évaluant son effet sur les paramètres tel que les événements cardio-vasculaires et la mortalité (toutes causes confondues) manquent encore.

Traduit par Suzanne Laplante