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

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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 Eli Lilly and Company and Amylin Pharmaceuticals were contacted for additional unpublished information.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.

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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] Alternatives 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

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

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-relase exenatide 10 µg.[22] The median half-life of exenatide once weekly is approximately 2 weeks. After discontinuation, concentrations

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-1[21] and DURATION-5[23] 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 exe-

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.

[c] Although DURATION-2 evaluated the effects of the study drugs on lipids and blood pressure, numeric values were not reported in the article.

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 in the insulin glargine arm withdrew due to lack of glycemic control (6.3% vs 0.7%). 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. Concensus 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 con-

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