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REVIEW

Exenatide: Review of its Role as Adjunctive Therapy in Patients with Type 2 Diabetes

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Abstract: Exenatide was the first glucagon like peptide-1 (GLP-1) agonist approved for treatment in patients with type 2 diabetes. Clinical trials and real-world studies of exenatide, a subcutaneous injection given twice per day, indicate that it significantly reduces hemoglobin A1c values and weight with a low risk of hypoglycemia. Exenatide is generally well tolerated, but transient nausea and vomiting are commonly occurring side effects. Given this profile, exenatide has been shown to be cost effective relative to insulin glargine. Thus, exenatide is a treatment option that should be considered for patients with type 2 diabetes that is uncontrolled on one or more oral agents and for which additional weight gain and hypoglycemia are undesirable.

Keywords: exenatide, type 2 diabetes, adjunctive therapy, glycemic control, hypoglycemia, weight change

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Introduction

Diabetes currently affects almost 26 million people in the US, or more than 8% of the population.[1] The total estimated cost of diabetes in the US in 2007 was $174 billion dollars.[2] The estimated lifetime risk of developing diabetes for individuals born in 2000 is 33% for males and 39% for females.[3] Thus the prevalence and the corresponding health and economic burden of diabetes is expected to increase.

Approximately 95% of patients with diabetes have type 2 diabetes (T2DM).[1] Unlike type 1 diabetes that results from a deficiency of insulin production due a selective autoimmune destruction of pancreatic beta cells, T2DM often begins with insulin resistance at target tissues, mainly adipose and skeletal muscle tissue. This leads to reduced insulin production due to damage to the pancreas and elevated levels of glucagon cause fasting and postprandial hyperglycemia.[4–6] Initially, increased insulin production is able to compensate for hyperglycemia. However, insulin resistance can occur for years and persistent increased production can exhaust the pancreas leading to decreased insulin secretion.

Patients with diabetes have higher rates of related comorbidities, such as obesity, hypertension, and hyperlipidemia that are often present in individuals with T2DM.[7–11] Given the pathophysiology of diabetes and these complications, diabetes is the leading cause of blindness in adults, and is the leading cause of kidney failure in the US.[1] Furthermore, the risk of death from heart disease and stroke is 2 to 4 times higher in those with diabetes than for those without diabetes.[1] Fortunately, effective management of hyperglycemia associated with T2DM reduces the risk of serious complications. In a recent meta-analysis of clinical trials, patients treated with intensive glucose lowering had lower HbA1c values and fewer non-fatal myocardial infarctions and less coronary heart disease than those receiving standard treatment.[12]

However, the results from the Veterans Affairs Diabetes Trial (VADT) included in the meta-analysis showed that intensive glucose control may not reduce the risk of cardiovascular disease or death[13] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial actually showed that intensive glucose control increased all-cause mortality and death from myocardial infarction.[14,15] The reasons for the increased risk of mortality observed in the ACCORD trial remain unclear, with evidence suggesting that excess mortality is not completely attributable to severe hypoglycemia or reduction in HbA1c.[15–17] However, other factors such as weight gain have not been fully assessed. While controversy remains over the risks and benefits of aggressive and intense glucose control in patients with existing T2DM, the benefits of effective of blood glucose management remain undisputed.

As type 2 diabetes is a complex disease there are many potential drug targets and a variety of therapies used to manage the disease. Many of these treatments can be categorized as insulin secretagogues and insulin sensitizers. Insulin secretagogues include sulfonylureas and meglitinides which act on pancreatic beta cells to increase the release of insulin.[18–20] The major side effects of these treatments are a result of increased insulin secretion and include weight gain and hypoglycemia. Treatment with most of the insulin analogues also causes these side effects. Insulin sensitizers such as the biguanide metformin and thiazolidinediones (TZDs) do not cause insulin secretion and thus do not exhibit some of the same side effects. Metformin acts on the liver and muscle tissues, reducing glucose production and increasing insulin sensitivity.[21] Metformin is considered to be weight neutral, but has a risk of lactic acidosis and should not be used in patients with impaired renal function. TZDs are agonists for nuclear peroxisome proliferator-activated receptor-ϒ (PPAR-ϒ) which activates genes to regulate carbohydrate and lipid metabolism.[22] Ultimately, TZDs increase insulin sensitivity but can cause edema and weight gain.

There are several newer therapies with different mechanisms of action that do not cause the side effects of the above listed therapies. Amylin mimetics, such as pramlintide, act on the gut to slow gastric emptying and suppress appetite and to inhibit glucagon secretion from the pancreas.[23] Pramlintide is approved for use in conjuction with insulin to treat type 1 and type 2 diabetes.[23] When given with insulin, pramlintide increases the risk of severe hypoglycemia and because of this a 50% reduction in the meal time dose of insulin is recommended when pramlintide is started.[23]

Incretin hormones are endogenous gastrointestinal hormones that increase insulin and decrease glucagon

secretion in the presence of glucose. Incretin mimetics or glucagon-like peptide-1 (GLP-1) receptor agonists were developed to replicate the actions of incretin hormones. Incretin hormones induce glucose stimulated insulin release, inhibit gastric emptying, and suppress post-prandial glucagon levels.[24–29] Lactic acidosis and edema are not seen with the GLP-1 agonists and prevalence of hypoglycemia is low. Dipeptidyl peptidase-4 (DPP-4) is an enzyme that breaks down incretin hormones. DPP-4 inhibitors prevent the breakdown of endogenous GLP-1 increasing serum concentrations.[30] They are considered weight neutral and hypoglycemia is not typically seen during treatment.

This review specifically examines the literature surrounding the use of exenatide. Exenatide was the first GLP-1 agonist approved for use in patients with T2DM.

Exenatide

Pharmacology

Exenatide is a synthetic incretin mimetic that was derived from the venom of the Gila monster.[31] Exenatide induces glucose stimulated insulin release, but works only in the presence of glucose thereby reducing the risk of hypoglycemia.[24] Exenatide also inhibits gastric emptying causing a decrease in meal-related glucose concentrations.[25,26,32] Furthermore, exenatide suppresses post-prandial glucagon levels decreasing the amount of endogenous hepatic glucose being released,[27–29] and exhibits appetite suppressant effects and causes early satiety.[33]

Indication and dosing

Exenatide is currently approved to treat type 2 diabetes in patients not adequately controlled with or without oral agents and is given twice per day via subcutaneous injection before the morning and evening meals.[34] The initial dose is 5 mcg twice daily and is given for four weeks then the dose is increased to 10 mcg twice daily as needed for clinical response.

This review discusses clinical trial and real-world study data related to the efficacy and effectiveness of exenatide in the treatment of type 2 diabetes. It also reviews the pharmacoeconomic and safety data related to exenatide, and discusses this product's role in therapy in light of the available evidence.

Clinical Studies

Clinical trials have demonstrated the efficacy and safety of using exenatide in the treatment of T2DM (Table 1). Exenatide elicits a significant improvement in glycemic control, including postprandial glucose concentration,[35,36] and many patients treated with exenatide experience significant weight loss.[37–42] Furthermore, exenatide has also shown to have a positive effect on blood pressure in hypertensive patients,[37,38,43] but there are no consistent trends in regards to exenatide's effect on lipids.[44–48]

Numerous studies have compared exenatide to placebo[49–52] or insulin[47,53–55] in patients receiving metformin and/or sulfonylureas. Over all of the studies, patients receiving exenatide had significant reductions in HbA1c ranging from –0.4% to –1.2%, and all reductions were significantly greater than placebo.

When exenatide was used in the absence of other therapy, patients experienced a reduction in HbA1c ranging from –0.7% with 5 mcg twice daily to –0.9% with 10 mcg twice daily.[46] In patients receiving ongoing metformin, sulfonylurea, or thiazolidinedione (TZD) treatment, the response to exenatide was, similar, ranging from –0.4% to –1.2%.[52–54,56]

The core clinical trials of exenatide ranged from 16–30 weeks in duration. However, three of these trials evaluated the long-term effects of exenatide in open label extension trials conducted over a total of 82 weeks (52 week extension). Significant decreases in HbA1c were maintained over the 82 week period, with the change from baseline ranging from –0.7% to –0.8%.[44,57,58]

In the studies comparing exenatide to insulin in patients maintained on oral therapy or when insulin was replaced with exenatide, HbA1c decreases with exenatide were generally more pronounced than observed in placebo controlled trials ranging from –1.04% to –1.75%. However, exenatide showed no statistically significant benefit over insulin in terms glycemic response, and in one study versus biphasic insulin aspart, HbA1c reduction was greater with insulin.[47,53–55,59]

Many clinical trials also measured exenatide's effect on postprandial glucose levels.[46,47,50–56,59] Exenatide demonstrated a significantly greater reduction in postprandial glucose concentration than placebo or insulin in all but one of the trials in which

Table 1. Clinical studies.

Reference	Study design	N	Treatment regimen	Δ A1c
Added to metformin and/or a sulfonylurea				
Buse et al[49]	30 week, randomized, triple-blind, placebo controlled study	377	EXEN 5 or 10 mcg BID vs. PCB added to maximum dose of SU	EXEN 5 mcg: –0.46% EXEN 10 mcg: –0.86% PCB: +0.12% Adjusted $P \leq 0.0002$ for pairwise comparisons
DeFronzo et al[50]	30 week, randomized, triple-blind, placebo controlled study	336	EXEN 5 or 10 mcg BID vs. PCB added to MET	EXEN 5 mcg: –0.4% EXEN 10 mcg: –0.8% PCB: +0.1% Both EXEN 5 mcg and 10 mcg vs. PCB: $P < 0.0005$
Kendall et al[51]	30 week, randomized, double-blind, placebo controlled study	733	EXEN 5 or 10 mcg BID vs. PCB added to MET and either max or min dose of SU	EXEN 5 mcg: –0.55%, vs. PCB: $P < 0.0001$ EXEN 10 mcg: –0.77%, vs. PCB: $P < 0.0001$ PCB: +0.23%
Blonde et al[58]	52 week, open-label, uncontrolled, extension of DeFronzo,[50] Kendall,[51] and Buse[49]	ITT = 551 Comp = 314	EXEN 10 mcg BID added to MET and/or SU	At week 82 from baseline: ITT: –0.8% [95% CI –0.6% to –0.9%] Comp: –1.1% [95% CI –1.0% to –1.3%]
Ratner et al[44]	52 week, open-label, uncontrolled, extension of DeFronzo[50]	ITT = 150 Comp = 92	EXEN 10 mcg BID added to MET	At week 82 from baseline: ITT: –0.8% [95% CI –1.0 to –0.6], $P < 0.05$ Comp: –1.3% [95% CI –1.5 to –1.0], $P < 0.05$
Riddle et al[57]	52 week, open-label, uncontrolled, extension of Kendall[51] and Buse[49]	ITT = 401 Comp = 222	EXEN 10 mcg BID added to MET and/or SU	At week 82 from baseline: ITT: –0.7% [95% CI –0.6 to –0.9] Comp: –1.0% [95% CI –0.9 to –1.2]
Gao et al[52]	16 week, randomized, double-blind, placebo controlled study in patients of Asian descent	466	EXEN 10 mcg BID vs. PCB added to MET with or without a SU	EXEN: –1.2% PCB: –0.4% Difference: –0.9% [95% CI –1.0 to –0.7] $P < 0.001$
Added to thiazolidinediones				
Zinman et al[56]	16 week, randomized, double-blind, placebo controlled study	233	EXEN 10 mcg BID vs. PCB added to a TZD with or without MET	EXEN: –0.89% PCB: +0.09% Difference: –0.98% [95% CI –1.21 to –0.74]
Compared to insulin				
Heine et al[53]	26 week, randomized, open-label, controlled study	551	EXEN 10 mcg BID vs. GLAR QD added to maximum doses of MET and a SU	EXEN: –1.11% GLAR: –1.11% Difference: 0.017% [95% CI –0.12 to 0.16]

Weight change	Blood pressure	Hypoglycemia	Adverse effects
EXEN 5 mcg: –0.9 kg, vs. PCB: P = NS EXEN 10 mcg: –1.6 kg, vs. PCB: $P < 0.05$ PCB: –0.6 kg	NR	EXEN 5 mcg 14%, EXEN 10 mcg 36%, and PCB 3%; 50% SU dose reduction if hypoglycemia occurred	Nausea: EXEN 5 mcg 39%, EXEN 10 mcg 51%, and PCB 7%
EXEN 5 mcg: –1.6 kg, vs. PCB: $P \leq 0.05$ EXEN 10 mcg: –2.8 kg, vs. PCB: $P \leq 0.001$ PCB: –0.3 kg	NR	EXEN 5 mcg 5%, EXEN 10 mcg 5%, and PCB 5%	Nausea: EXEN 5 mcg 36%, EXEN 10 mcg 45%, and PCB 23% Vomiting: EXEN 5 mcg 11%, EXEN 10 mcg 12%, and PCB 4%
EXEN 5 mcg: –1.6 kg, vs. PCB: $P \leq 0.01$ EXEN 10 mcg: –1.6 kg, vs. PCB: $P \leq 0.01$ PCB: –0.9 kg	NR	EXEN 5 mcg 19.2%, EXEN 10 mcg 27.8%, and PCB 12.6%; 50% SU dose reduction if hypoglycemia occurred	Nausea: EXEN 5 mcg 39.2%, EXEN 10 mcg 48.5%, and PCB 20.6% Vomiting: EXEN 5 mcg 14.7%, EXEN 10 mcg 13.7%, and PCB 4.5%
At week 82 from baseline: ITT: –3.5 kg [95% CI –3.1 to –4.0] Comp: –4.4 kg [95% CI –3.8 to –5.1]	At week 82 from baseline: ITT: NR Comp: SBP –1.3 mmHg [95% CI –3.1 to 0.5] DBP –2.7 mmHg [95% CI –3.8 to –1.7]	At week 82, ITT: 10%	At week 82, ITT: Nausea 15%
At week 82 from baseline: ITT: –4.3 kg [95% CI –5.5 to –3.2], $P < 0.05$ Comp: –5.3 kg [95% CI –7.0 to –3.7], $P < 0.05$	At week 82 from baseline: ITT: NR Comp: SBP –6.3 mmHg [95% CI –9.4 to –3.1] DBP –4.1 mmHg [95% CI –6.1 to –2.2]	"Rare"	At week 82, ITT: Nausea 14% Vomiting 1%
At week 82 from baseline: ITT: –3.3 kg [95% CI –3.7 to –2.8] Comp: –4.0 kg [95% CI –4.6 to –3.4]	NR	At week 82, ITT: 14%	At week 82, ITT: Nausea 15%
EXEN: –1.2 kg PCB: –0.1 kg Difference: –1.0 [95% CI –1.4 to –0.6], $P < 0.001$	NR	EXEN 35.5% vs. PCB 9.1%, $P < 0.001$; consider 50% reduction in SU dose if hypoglycemia occurred	Nausea: EXEN 25.2% and PCB 0.9% Vomiting: EXEN 15.8% and PCB 0.0%
EXEN: –1.75 kg PCB: –0.24 kg Difference: –1.51 kg [95% CI –2.15 to –0.88]	NR	EXEN vs. PCB 3.6% [95% CI –4.6% to 11.8%]	Nausea: EXEN vs. PCB 24.5% [95% CI 12.7 to 36.3] Vomiting: EXEN vs. PCB 12.3% [95% CI 5.2 to 19.5]
EXEN: –2.3 kg GLAR: +1.8 kg Difference: –4.1 kg [95% CI –4.6 to –3.5]	NR	EXEN vs. GLAR difference –1.1 events/patient-year [95% CI –1.3 to 3.4]; 50% SU dose reduction if hypoglycemia occurred	Nausea: EXEN 57.1% and GLAR 8.6% Vomiting EXEN 17.1% and GLAR 3.7%

(*Continued*)

Table 1. (*Continued*)

Reference	Study design	N	Treatment regimen	Δ A1c
Barnett et al[54]	32 week, randomized, open-label, non-inferiority, crossover study	138	EXEN 10 mcg BID vs. GLAR QD cross-over added to MET or SU	EXEN: –1.36% GLAR: –1.36% Ending difference: –0.01% [95% CI –0.17 to 0.15]
Davis et al[59]	16 week, randomized, open-label, parallel-group study	49	Continue INS regimen or switch to EXEN 10 mcg BID with MET and/or a SU	EXEN: +0.3%, P = NS INS: –0.1%, P = NS
Nauck et al[47]	52 week, randomized, open-label, noninferiority study	501	EXEN 10 mcg BID vs. BIAsp BID added to "optimally effective doses" of MET and SU	EXEN: –1.04% BIAsp: –0.89% Difference: –0.15% [95% CI –0.32 to 0.01] P = 0.067
Bergenstal et al[55]	24 week, randomized, open-label, parallel-group study in insulin naïve patients	372	EXEN 10 mcg BID vs. BIAsp QD or BIAsp BID added to MET and a SU	EXEN: –1.75% BIAsp QD: –2.76%, vs. EXEN $P < 0.001$ BIAsp BID: –2.34%, vs. EXEN $P < 0.001$
Exenatide monotherapy				
Moretto et al[46]	24-week, randomized, double-blind, placebo controlled, parallel-group study	232	EXEN 5 mcg or 10 mcg BID vs. PCB without any other antidiabetic medications	EXEN 5 mcg: –0.7%, vs. PCB: P = 0.003 EXEN 10 mcg: –0.9%, vs. PCB: $P < 0.001$ PCB: –0.2%

postprandial glucose was measured. In the remaining study, biphasic insulin demonstrated lower postprandial glucose concentrations than exenatide.[55]

A notable benefit of GLP-1 therapy is its positive impact on weight. Mean, significant weight loss with exenatide ranged from –0.9 kg to –4.2 kg in short-term studies,[46,47,49–56,59] which was significantly greater than placebo in all but one study.[49] The open label extension trials demonstrated that weight loss with exenatide appears to be progressive with patients losing from –3.3 kg to –5.3 kg total weight loss over the 82-week period, versus –0.9 kg to –2.8 kg at the end of the 26-week placebo controlled phase.[44,57,58] In contrast, in all of the studies where exenatide was compared to insulin, patients receiving insulin had mean weight increases ranging from 0.5 kg to 4.1 kg.[47,53–55,59]

A small number of trials reported blood pressure outcomes in addition to glycemic control and weight, with blood pressure reductions modest and inconsistent in regards to both clinical and statistical significance.[44,46,47,58] Systolic blood pressure (SBP) reduction ranged from –1.3 mmHg to –6.3 mmHg while diastolic blood pressure (DBP) reduction ranged from –0.8 mmHg to –4.1 mmHg. A recent pooled analysis of six trials has provided additional insight into the effects of exenatide on blood pressure.[43] Including 1,096 patients treated with exenatide and 1,075 treated with insulin or placebo for at least six months, this pooled analysis found that exenatide

Weight change	Blood pressure	Hypoglycemia	Adverse effects
E/G: –2.0 kg, +2.3 kg G/E: +1.0 kg, –2.2 kg EXEN vs. GLAR: $P < 0.001$	NR	EXEN 14.7% and GLAR 25.2%, P = NS; could reduce SU dose if hypoglycemia	Nausea: EXEN 42.6% and GLAR 3.1% Vomiting: EXEN 9.6% and GLAR 3.1%
EXEN: –4.2 kg INS: +0.5 kg Difference: $P < 0.001$	NR	EXEN 39% and INS 38%	Nausea: EXEN 48.5% and INS 12.5%
EXEN: –2.5 kg BIAsp: +2.9 kg Difference: –5.4 kg [95% CI –5.9 to –5.0] $P < 0.001$	EXEN: SBP –5 mmHg, $P < 0.001$; DBP –2 mmHg, $P = 0.03$ BIAsp: SBP 1 mmHg, P = NS; DBP 1 mmHg, P = NS	EXEN 4.7 events/patient-year and BIAsp 5.6 events/patient-year; 50% SU dose reduction if hypoglycemia occurred	Nausea: EXEN 33.2% and BIAsp 0.4% Vomiting: EXEN 15.0% and BIAsp 3.2%
EXEN: –1.96 kg BIAsp QD: +2.85 kg BIAsp BID: +4.08 kg	NR	EXEN 29%, BIAsp QD 56%, and BIAsp BID 61%; BIAsp BID discontinued SU at beginning of study	GI events: EXEN 29%, BIAsp QD 9%, and BIAsp BID 8%
EXEN 5 mcg: –2.8 kg, vs. PCB: $P = 0.004$ EXEN 10 mcg: –3.1 kg, vs. PCB: $P < 0.001$ PCB: –1.4 kg	EXEN 5 mcg: SBP –3.7 mmHg, vs. PCB $P = 0.037$; DBP –0.8 mmHg, vs. PCB P = NS EXEN 10 mcg: SBP –3.7 mmHg, vs. PCB $P = 0.037$; DBP –2.3 mmHg, vs. PCB $P = 0.046$ PCB: SBP –0.3 mmHg, DBP –0.3 mmHg	EXEN 5 mcg 5%, EXEN 10 mcg 4%, and PCB 1%	Nausea: EXEN 5 mcg 3%, EXEN 10 mcg 13%, and PCB 0%; combined EXEN vs. PCB $P = 0.010$ Vomiting: EXEN 5 mcg 4%, EXEN 10 mcg 4%, and PCB 0%

Abbreviations: 95% CI, 95% confidence interval; EXEN, exenatide; BID, twice per day; BIAsp, biphasic insulin aspart 70/30; QD, daily; GLAR, insulin glargine; INS, insulin; NS, not significant; E/G, received exenatide then insulin glargine; G/E, received insulin glargine then exenatide; PCB, placebo; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione; SITA, sitagliptin; PIO, pioglitazone; NR, not reported; ITT, intention to treat; Comp, completer group.

elicited a significantly greater reduction in SBP than placebo (difference: –2.8 mmHg, $P < 0.001$) and insulin (difference: –3.7 mmHg, $P < 0.001$), but no significant difference was seen in DBP. Possibly more interesting was the finding that blood pressure reduction was dependent on baseline blood pressure. Patients with higher baseline blood pressures saw greater reductions, with patients with elevated systolic blood pressure (e.g. >150 mmHg) experiencing a reduction in systolic blood pressure of –22.5 mmHg (–8.2 mmHg vs. placebo).

In summary, the data from the clinical trials demonstrate the efficacy of exenatide in reducing HbA1c values when used alone or as adjunctive treatment. Clinical trial data also show that exenatide effectively reduces postprandial glucose concentrations and causes significant weight loss. Among clinical trials, exenatide has had mixed results as it pertains to blood pressure, but the pooled analysis shows exenatide reduces SBP, particularly in those with elevated blood pressure.

Safety and Adverse Effects

Common adverse effects seen with exenatide include hypoglycemia, particularly when given with a sulfonylurea, nausea and vomiting, and injection site reactions.[34] Nausea and vomiting are most prevalent at the beginning of treatment and generally decrease as treatment continues. In every clinical trial evaluated, including studies of unapproved indications, the rates of nausea

Table 2. Retrospective outcomes and pharmacoeconomic studies.

Reference/country	Study design outcomes period/ time horizon	Population
Retrospective outcomes studies		
Bhushan[41] US	Retrospective; 16 weeks	N = 176, treated with exenatide from 2005–2007, with type 2 diabetes and metabolic syndrome
Brixner[37] US	Retrospective, 6-month study	N = 1709, with type 2 diabetes, baseline HbA1c >7.0%, treated with exenatide (2+ prescriptions)
Fabunmi[68] US	Retrospective; 1 year	N = 3262 patients with type 2 diabetes started on exenatide and N = 3038 on glargine from 2005–2007
McAdam-Marx[38] US	Retrospective 18 month	N = 118 patients with type 2 diabetes, baseline HbA1c >7.0%, treated with exenatide (2+ prescriptions)
Sheffield[69] US	Retrospective; 12+ months	N = 134 patients with type 2 diabetes on insulin who were started on exenatide from 2005–2006
Yoon[70] US	Retrospective; outcomes evaluated at months 0–6, 6–12, 12–18, 18–27 months	N = 268 patients on insulin receiving adjunct exenatide therapy
Economic analyses		
Models		
Brandle[74] Switzerland	CORE diabetes simulation model 35-year horizon	Patients with type 2 diabetes, mean age 59 years, diabetes duration 10 years, HbA2c 8.2%
Mittendorf[77] Germany	CORE diabetes model; 10-year horizon	Patients with type 2 diabetes, mean age 59 years, duration of diabetes 10 years, HbA1c 8.2%

Data source/inputs	Treatment regimen*	Outcomes
Endocrinology clinic chart review	Exenatide twice-daily added to oral agents or insulin	Mean (sd) parameters at baseline to follow-up: HbA1c; 7.2% (0.12) to 6.9% (0.11) ($P < 0.001$) Percent who achieved HbA1c <7.0%; 68% Weight: 106 (1.8) kg to 104 (1.7) kg ($P < 0.001$) Percent of patients who lost weight; 76% Blood pressure: Not significant
National electronic medical record database	Exenatide twice daily added to oral agents	HbA1c reduction (s.e.m.): –0.8% (0.05) ($P < 0.001$) Weight loss: –3.2 kg (0.14) ($P < 0.001$), Systolic blood pressure reduction: –1.9 mmHg (0.46) ($P < 0.001$) Diastolic blood pressure reduction: –0.5 mmHg (0.27) ($P = 0.078$).
US medical and pharmacy claims database	Exenatide or glargine (with or without oral agents)	Number (%) of patients experiencing a hypoglycemic event exenatide vs. glargine: 138 (4.2%) vs. 212 (7.0%) ($P < 0.001$)
National electronic medical record database	Exenatide twice daily added to oral agents	HbA1c reduction (s.e.m): –0.7% (0.2) ($P < 0.001$) Weight loss: –4.7 kg (0.7) ($P < 0.001$)
Endocrinology clinic chart review	Exenatide + insulin	HbA1c reduction: –0.87% ($P < 0.001$) Mean weight loss: 5.2 kg ($P < 0.001$), Percent of patients who lost weight: 72%. Number (%) experiencing hypoglycemia: 14 (10%)
Endocrinology clinic chart review	Exenatide + insulin	Mean (sd) change in HbA1c from baseline: 0–6 months: –0.66% (1.54%) ($P < 0.001$) 6–12 months: –0.55% (1.4%) ($P < 0.001$) 12–18 months: –0.54% (1.83%) ($P = 0.019$) 18–27 months: –0.54% (1.37%) ($P = 0.020$). Mean change in weight from baseline 0–6 months: –2.4 (5.1) kg ($P < 0.001$) 6–12 months: –4.3 (7.2) kg ($P < 0.001$) 12–18 months: –6.2 (9.7) kg ($P < 0.001$) 18–27 months: –5.5 (10.8) kg ($P < 0.01$). Of all included patients; 9 (4.0%) were discontinued due to hypoglycemia
Clinical data from 26-week clinical trial; cost data from published sources	Exenatide or glargine; added to oral agents	Outcomes (exenatide vs. glargine) in Swiss Francs (CHF) Quality adjusted life expectancy 7.94 vs. 7.51 ($P = 0.43$) Exenatide direct costs CHF 107,903 vs. CHF 99,524 Exenatide (vs. glargine) cost per QALY CHF 19,450 (range 6,332 to dominated when BMI and nausea not considered)
Clinical data from a clinical trial; costs from German payer perspective, per published sources and expert opinion	Exenatide vs. glargine	Exenatide vs. glargine; costs in Euros € Total costs: €22,095 (±554) vs. €18,242 (±588) Quality adjusted life expectancy: 4.87 vs. 4.59 Cost per QALY: €13,746 (Range €8230–€30,249; dominant with increased blood glucose self monitoring in glargine group; dominated when weight and nausea not considered)

(*Continued*)

Table 2. (*Continued*)

Reference/country	Study design outcomes period/ time horizon	Population
Ray[78] UK	CORE diabetes model; 35-year horizon	Patients with type 2 diabetes, mean age 59 years, duration of diabetes 10 years, HbA1c 8.2%
Woeh[79] UK	Discrete event simulation model; 40-year horizon	Patients with type 2 diabetes, mean age 59 years, HbA1c 7.1%
Lee[75]	IMS center for outcomes research diabetes model; 35-year horizon	Patients with type 2 diabetes, mean age 57 years, diabetes duration 8 years, HbA2c 8.2%
Minshall[76] US	CORE diabetes model; 30-year horizon	Patients with type 2 diabetes, mean age 56 years, diabetes duration 7 years, HbA2c 8.3%
Database analyses		
Lage[72] US	Retrospective; 6-month	Patients initiated on exenatide (n = 1885) or sitagliptin (n = 2482) from 2005–2007
Misurski[73] US	Retrospective; 12-month	Patients started on exenatide (n = 4090) or glargine (n = 1660) from 2005–2007

Data source/inputs	Treatment regimen*	Outcomes
Clinical data from 26-week clinical trial; UK-specific costs from published sources	Exenatide vs. glargine (added to oral agents)	Exenatide vs. glargine; costs in British Pounds Total direct costs: £29,401 (±676) vs. £19,489 (±636) Quality adjusted life expectancy: 7.39 vs. 6.95 Cost per QALY: £29,401 (Range: £7000–£39,763 when weight and nausea not considered)
Clinical data from 26-week clinical trial; UK-specific costs from published sources	Exenatide vs. glargine	Exenatide vs. glargine; costs in British Pounds No discontinuation: Total costs: £14,568 vs. £9280 Quality adjusted life expectancy: 7.68 vs. 7.86 Cost per QALY: –£29,149 (dominated) Range: –£4579 when failures excluded to –£29,657 when exenatide failures switched glargine.
Clinical data from 26-week clinical trial; costs from published sources.	Exenatide or liraglutide; added to oral agents	Outcomes (exenatide vs. liraglutide) in US$ Quality adjusted life expectancy 8.14 vs. 8.46; Direct costs $112,331 vs. $125,287 Liraglutide (vs. exenatide) cost per QALY $40,282 (range $33086–$55,470)
Clinical data from 82-week clinical trial; costs from Medicare perspective.	Exenatide vs. no additional antidiabetic therapy	Exenatide vs. non-exenatide; Total costs: $82,281 (±2401) vs. $67,531 (±2438) Quality adjusted life expectancy: 6.33 vs. 5.81 Cost per QALY: $36,133 (Range $20,548–$47,981)
US medical and pharmacy claims database	Exenatide or sitagliptin; added to other oral agent	Total (adjusted) direct costs (US$) exenatide vs. sitagliptin Inpatient: $2030 (±504) vs. $2424 (±2698); $P = 0.05$ Outpatient: $4498 (±4462) vs. $5942 (±12,025) ($P < 0.001$) Drug: $3603 (±802) vs. $3611 (±861) ($P = 0.73$) Total: $9340 (±3914) vs. $9995 (±6718) ($P < 0.001$) Diabetes related costs: Inpatient: $1098 (±118) vs. $1236 (±1386) ($P = 0.20$) Outpatient: $1444 (±822) vs. $1415 (±1002) ($P = 0.29$) Drug: $1765 (±302) vs. $1743 (±216) ($P = 0.006$) Total: $4141 (±897) vs. $4002 (±944) ($P < 0.001$)
US medical and pharmacy claims database	Exenatide or glargine; with or without oral agents	Total (adjusted) direct costs (US$) exenatide vs. glargine Inpatient: $4121 (4052–4190) vs. $7532 (7329–7735) ($P \leq 0.001$) Outpatient: $9501 (9162–9840) vs. $12,885 (11,546–14,224) ($P < 0.001$) Drug: $6885 (6832–6938) vs. $5936 (5857–6015) ($P < 0.001$) Total: $19,293 (18,990–19,596) vs. $23,782 (22,761–24,802) ($P < 0.001$) Diabetes related costs: Inpatient: $2172 (2157–2187) vs. $3538 (3482–3594) ($P < 0.001$) Outpatient: $2739 (2703–2775) vs. $3538 (3482–3594) ($P < 0.001$) Drug: $3160 (3144–3176) vs. $2422 (2396–2448) ($P < 0.001$) Total: $7833 (7776–7890) vs. $8536 (8389–8683) ($P < 0.001$)

and vomiting were higher in patients taking exenatide than other treatment options.[44,46,47,49–65] Rates of nausea ranged from 3% to 57.1% and vomiting ranged from 1% to 18.6%. In one study comparing weekly vs. twice-daily exenatide dosing, nausea and vomiting were seen more frequently with twice-daily dosing.[62]

Hypoglycemia is observed with exenatide therapy, and is most likely to occur when exenatide is added to a sulfonylurea.[47,49,51–55,62,63,65] Among sulfonylurea-treated patients in clinical trials, rates of hypoglycemia ranged from 8% to 36% or 4.7 to 7.3 events/patient-year. Hypoglycemia rates were lower when sulfonylurea doses were reduced before exenatide was started.[62,65] Hypoglycemia was prevalent but less common in patients not receiving concomitant sulfonylurea therapy,[44,46,50,52,54,56,60–62,64,65] while the highest hypoglycemia rates (10% to 38%) were reported in studies in which hypoglycemia events were not stratified by baseline oral therapy.[57–59] Therefore, to reduce the risk of hypoglycemia, it is recommended that when adding exenatide to sulfonylurea therapy, the sulfonylurea dose be reduced by 50% initially, and titrated up as necessary and as tolerated.

Cases of acute pancreatitis have also been reported with exenatide use, which has been included as a warning in the exenatide label.[34] However, the causal nature of these events in exenatide patients has not been established as diabetes itself is a risk factor for acute pancreatitis. Two recent retrospective database studies have contributed to this discussion by evaluating the incidence of acute pancreatitis in over 35,000 exenatide treated patients relative to patients with diabetes not treated with exenatide. Both studies concluded that there is no increase in the risk of developing pancreatitis with exenatide use with odds/hazard ratios in both studies of 1.0 (95% CI 0.6–1.7 and 0.7–1.3).[66,67]

Retrospective Outcomes Analyses

Exenatide has also been evaluated in numerous retrospective analyses based on clinic electronic medical record or medical and pharmacy claims data. This review focuses on six retrospective studies that included 100 or more patients with T2DM and that evaluated glycemic control, weight change, blood pressure change, or the occurrence of hypoglycemic events over 16 weeks to 27 months (Table 2).[37,38,41,68–70] All studies conducted a pre-post evaluation of exenatide's effect on select study parameters. Of these, three evaluated exenatide when added to existing oral therapy or insulin,[37,38,41] and three specifically evaluated exenatide when added to insulin.[68–70] Of the insulin studies, one compared outcomes with exenatide to insulin glargine.[68]

Of five studies that evaluated glycemic control,[37,38,41,69,70] all observed that exenatide therapy was associated with significant reductions in HbA1c ranging from –0.3% to –0.9%. Most of the effect on glycemic control was similar to efficacy observed in clinical trials with the exception of one study that observed a smaller reduction of –0.3%. However, baseline HbA1c in this study was 7.2% versus 8.0% or greater in the other studies that evaluated glycemic control. Reduction in glycemic control was consistent across studies of different time lengths and at different times within the same population[69] or population subset.[38]

The same five studies evaluated weight change and, like clinical trials, observed a reduction in weight with exenatide therapy.[37,38,41,69,70] Weight reduction ranged from –2 kg at 16 weeks to over –6 kg at 12–18 months. The continuation of weight loss observed in the real-world studies is similar to what was seen in clinical trials.[44,58]

Blood pressure outcomes were reported in two retrospective studies,[37,41] and, like the clinical trial data, results were inconsistent. One study found no difference in systolic or diastolic blood pressure with exenatide therapy,[41] while the second study identified a significant reduction in systolic blood pressure (–1.9 mmHg; $P < 0.01$) but no change in diastolic blood pressure. However, mean systolic blood pressures were near target level[71] of <130 mmHg (mean of 130 mmHg and 133 mmHg) and mean diastolic levels were below the 80 mmHg target (mean 75 mmHg and 76 mmHg); blood pressure outcomes were not reported by baseline blood pressure. A recent meta-analysis of clinical trial data, as discussed above, found that blood pressure reduction appears to occur in patients with elevated blood pressure but not necessarily in normotensive patients,[43] which may help explain why an effect on blood pressure was generally not observed in exenatide retrospective analyses.

Hypoglycemic events were reported in two of the six retrospective studies.[68,69] The proportion of patients treated with exenatide and insulin experiencing at least one hypoglycemic event was evaluated in one

study which found that 10% of patients experienced hypoglycemia.[69] Relative to insulin glargine, hypoglycemia occurred less with exenatide (4.2% of exenatide patients vs. 7.0% of those treated with glargine; $P < 0.001$).[68]

Retrospective studies that specifically evaluated outcomes related to the use of exenatide with insulin also reported changes in baseline insulin and other antidiabetic use after exenatide was initiated.[69,70] Prandial insulin dose requirements were reduced in both studies. One study found a reduction in insulin dose of 35% at 12 months,[69] while the other saw a range in insulin dose reduction from 26% at 6–12 months to 56% at 18–27 months.[70] Total insulin dose reduction was also reduced by 18% at 0–6 months but dose differences were not statistically different from baseline after 12 months.[70] Sulfonylureas were discontinued in 59% of patients using a sulfonylurea when exenatide was initiated.[69]

In summary, exenatide treatment outcomes in the usual practice setting were quite consistent with clinical trial observations. As with trial data,[44,58] retrospective analyses identified durability in glycemic control for at least 18 months, and a progressive weight reduction over time. Blood pressure outcomes in retrospective analyses were similarly inconsistent, and warrant further investigation. Finally, a benefit of adding exenatide to insulin may be the ability to reduce insulin dose and/or the use of other oral agents without increasing the risk of hypoglycemia. However, more data on the use of exenatide with insulin is necessary to substantiate these initial findings.

Economic Evaluations

Database analyses

Two retrospective economic analyses of US medical and pharmacy claims data were identified that reported direct overall healthcare costs and diabetes-related costs for patients treated with exenatide.[72,73] One of these studies compared 6-month post initiation costs between patients with type 2 diabetes after adding either exenatide or sitagliptin to oral agents. Compared to those on sitagliptin, patients initiated on exenatide had higher adjusted diabetes-related costs ($4141 vs. $4002; $P < 0.001$) driven in part by higher drug costs. However, exenatide patients had lower overall healthcare costs ($9340 vs. $9995; $P < 0.001$) with costs lower in all cost categories except for drugs, which did not differ.

A second economic analyses based on US data evaluated costs between patients initiated on exenatide to patients started on glargine either as initial therapy or as added to other antidiabetic treatment. Over the first 12 months of treatment, diabetes-related costs were lower with exenatide than glargine ($7833 vs. $8536; $P < 0.001$). Although diabetes-related drug costs were higher with exenatide ($3160 vs. $2422; $P < 0.001$), inpatient and outpatient costs were significantly less. Overall healthcare costs followed the same pattern with exenatide patients having overall lower costs than glargine ($19,293 vs. $23,782; $P < 0.001$) driven by lower inpatient and outpatient costs which was somewhat offset by higher overall drug costs.

Economic models

A total of six studies reporting the results of economic modeling analyses from the US and Europe were identified.[74–79] All studies identified were cost effectiveness analyses and reported economic outcomes in terms of the cost per quality adjusted life year (QALY). A QALY is a unit of measure that reflects changes in life expectancy with an intervention that is adjusted by the corresponding change in quality of life.[80] The determination of cost effectiveness, or the willingness to pay per QALY gained, is subjective and varies by country. In the US, $50,000–$100,000 per QALY is commonly accepted as cost effective. In the UK, the National Institute for Health and Clinical Excellence (NICE) has defined a cost effectiveness threshold of £20,000 to £30,000 per QALY.[81] In all of the reviewed economic analyses, clinical effectiveness assumptions were based on controlled clinical trials and cost data obtained from published sources of payer reimbursement amounts, with one study supplementing published data with expert opinion.[77]

The most common comparison, reported in four studies, was between exenatide and glargine.[74,77–79] Three of the studies, which were conducted in Switzerland, Germany, and the UK, concluded that exenatide was cost effective relative to glargine with cost per QALY ranging from €13,764 to €29,401 (£34,631 at an exchange rate of 1.178 Euro to British Pound).[74,77,78] Cost effectiveness was sensitive to weight change and occurrence of nausea. When these factors were ignored, costs per QALY for

Table 3. Future directions—clinical studies.

Reference	Study design	N	Treatment regimen	Δ A1c	Weight change
Added to insulin					
Buse et al[60]	30 week, randomized, parallel-group, placebo-controlled study	261	EXEN 10 mcg BID or PCB added to GLAR alone or in combination with MET and/or PIO	EXEN: –1.74% PCB: –1.04% difference: –0.69% [95% CI –0.93 to –0.46], $P < 0.001$	EXEN: –1.78 kg PCB: +0.96 kg difference: –2.74 kg [95% CI –3.74 to –1.74], $P < 0.001$
Once weekly dosing					
Kim et al[61]	15 week, randomized, placebo-controlled phase 2 trial	45	EXEN 0.8 or 2 mg QW vs. PCB with or without MET	EXEN 0.8 mg: –1.4%, vs. PCB: <0.05 EXEN 2 mg: –1.7%, vs. PCB: <0.05 PCB: +0.4%	EXEN 0.8 mg: –0.04 kg, vs. PCB $P = NS$ EXEN 2 mg: –3.8 kg, vs. PCB $P < 0.05$ PCB: –0.03 kg
Drucker et al[62]	30-week, randomized, controlled, open-label, non-inferiority study	295	EXEN 10 mcg BID vs. EXEN 2 mg QW added to MET, SU, or TZD alone or in combination	EXEN BID: –1.5% EXEN QW: –1.9% difference –0.33% [95% CI –0.54 to –0.12], $P = 0.0023$	EXEN BID: –3.7 kg EXEN QW: –3.6 kg difference –0.1 kg [95% CI –1.3 to 1.1]
Iwamoto et al[63]	10 week, randomized, placebo-controlled, double-blind, parallel study in Japanese patients	30	EXEN 0.8 or 2 mg QW vs. PCB added to MET, SU, or TZD alone or in combination	EXEN 0.8 mg: –1.0% EXEN 2 mg: –1.5% PCB: –0.4%	EXEN 0.8 mg: +0.3 kg EXEN 2 mg: –0.8 kg PCB: –1.6 kg
Bergenstal et al[64]	26-week, randomized, double-blind, double-dummy study	491	EXEN 2 mg QW vs. SITA QD or PIO QD added to MET	EXEN: –1.5% SITA: –0.9% PIO: –1.2% EXEN vs. SITA: $P < 0.001$ EXEN vs. PIO: $P = 0.0165$	EXEN: –2.3 kg SITA: –0.8 kg PIO: +2.8 kg EXEN vs. SITA: $P < 0.001$ difference: –1.5 kg [95% CI –2.4 to –0.7] EXEN vs. PIO: $P < 0.001$ difference –5.1 kg [95% CI –5.9 to –4.3]
Buse et al[65]	22 week extension of Drucker[62]	258	Continue EXEN QW or EXEN BID Δ to QW added to MET, SU, or TZD alone or in combination	At week 52 from baseline: QW only: –2.0% [95% CI –2.1 to –1.8] Δ to QW: –2.0% 95% CI NR	At week 52 from baseline: QW only: –4.1 kg [95% CI –5.3to –2.9] Δ to QW: –4.5 kg [95% CI –5.7 to –3.3]

exenatide were notably higher if not dominated by glargine. The fourth study, which was also from the UK, found that exenatide was dominated by glargine (e.g. glargine was more effective and cost less). The reason these studies reached different conclusions may be related to the modeling approach. The studies finding exenatide to be cost effective relative to glargine were based on the CORE diabetes model (a Markov event-state model). The study concluding that glargine dominated exenatide was based on a different model and modeling technique (a discrete event model). While many parameters were similar

Blood pressure	Hypoglycemia	Adverse effects
EXEN: SBP –2.7 mmHg, DBP –1.7 mmHg PCB: SBP 1.7 mmHg, DBP 1.7 mmHg SBP difference: –4.4 mmHg [95% CI –7.8 to –1.0], $P = 0.01$; DBP difference: –3.4 mmHg [95% CI –5.2 to –1.6], $P < 0.001$	EXEN 25% vs. PCB 29%; EXEN 1.4 events/patient-year vs. PCB 1.2 events/patient-year, P = NS	Nausea: EXEN vs. PCB 32% [95% CI 23% to 42%] Vomiting: EXEN vs. PCB 14% [95% CI 7% to 21%]
NR	EXEN 0.8 mg 25%, EXEN 2 mg 0%, and PCB 0%	Nausea: EXEN 0.8 mg 19%, EXEN 2 mg 27%, and PCB 15%
EXEN BID: SBP –3.4 mmHg [95% CI –5.5 to 1.3], DBP –1.7 mmHg [95% CI –3.1 to –0.3] EXEN QW: SBP –4.7 mmHg [95% CI –6.9 to –2.6], DBP –1.7 mmHg [95% CI –3.1 to –0.3]	Hypoglycemia among SU treated patients: EXEN BID 15.4% and EXEN QW 14.5%; SU dose was decreased to min until week 10, then it could be up-titrated	Nausea: EXEN BID 34.5% and EXEN QW 26.4% Vomiting: EXEN BID 18.6% and EXEN QW 10.8%
NR	EXEN 0.8 mg 10%, EXEN 2 mg 11%, and PCB NR	Nausea: EXEN 0.8 mg NR, EXEN 2 mg 33%, and PCB NR Vomiting: EXEN 0.8 mg NR, EXEN 2 mg 11%, and PCB 10%
EXEN vs. SITA: SBP difference –4 mmHg [95% CI –6 to –1], $P = 0.006$; DBP P = NS EXEN vs. PIO: SBP P = NS; DBP P = NS	EXEN 1%, SITA 3%, and PIO 1%	Nausea: EXEN 24%, SITA 10%, and PIO 5% Vomiting: EXEN 11%, SITA 2%, and PIO 3%
QW only: SBP –6.2 mmHg [95% CI –8.5 to –3.9], DBP –2.8 mmHg [95% CI –4.3 to –1.3] Δ to QW: SBP –3.8 mmHg [95% CI –6.1 to –1.5], DBP –1.8 mmHg [95% CI –3.2 to –0.3]	Hypoglycemia among SU treated patients: QW only 10.2% and Δ to QW 8.0%; Δ to QW decreased SU dose to min dose until week 40	From week 30 to week 52: Nausea: QW only 7.0% and Δ to QW 7.7% Vomiting: QW only 6.3% and Δ to QW 4.6%

Abbreviations: 95% CI, 95% confidence interval; EXEN, exenatide; BID, twice per day; QD, daily; GLAR, insulin glargine; INS, insulin; NS, not significant; PCB, placebo; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione; QW, weekly; SITA, sitagliptin; PIO, pioglitazone; NR, not reported.

between the approaches, including assumptions about the development of complications, which were all based on UKPDS data, the models generated different estimates for QALY gained. The core model estimated a greater QALY gain for exenatide while the discrete event model estimated a larger QALY gain for glargine. While the explanation for this scenario is beyond the scope of this article, it highlights the fact that modeling approaches can influence pharmacoeconomic conclusions.

One of the identified cost effectiveness analyses compared liraglutide, a newer GLP-1 agonist, to

exenatide.[75] This study found that the cost per QALY for liraglutide was US$40,282 relative to exenatide. While direct medical cost of therapy was lower for exenatide in this study, quality adjusted life years gained was greater with liraglutide. The final cost effectiveness study evaluated the cost per QALY for exenatide as compared to usual therapy (no addition of exenatide).[76] This study estimated that the cost per QALY for exenatide was US$36,133.

In summary, most economic analyses found that exenatide is cost effective relative to other treatment alternatives. However, cost effectiveness determinations were sensitive to weight outcomes and occurrence of side effects, notably nausea. When study funding is also considered, published results of all analyses favored the funding company's product. Thus, these findings likely reflect a publication bias with the studies evaluating the cost effectiveness of newer antidiabetic agents, including exenatide, and illustrate a need for economic analyses not funded by the pharmaceutical industry.

Place in Therapy

Two recently published consensus statements of the management of type 2 diabetes differ in their placement of GLP-1 agonists in treatment. In the consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), GLP-1 agonists are placed with tier 2 (less well-validated) therapies.[82] According to the ADA/EASD statement GLP-1 agonists should be added to lifestyle changes and metformin in select clinical settings such as "when hypoglycemia is particularly undesirable" or "promotion of weight loss is a major consideration".[82] If dual therapy does not bring the patient to a goal HbA1c of $<7\%$, then the consensus statement recommends metformin and intensive insulin therapy.

In contrast, the consensus statement from the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommends GLP-1 agonists or DPP-4 inhibitors to be considered second line, after metformin monotherapy when dual therapy is needed.[83] A higher preference is given to GLP-1 therapy due to its effects on post-prandial glucose and weight loss potential.[83] These classes are recommended in general because of safety, weight profiles, and effectiveness in reducing HbA1c. When triple therapy may be needed to bring patients to a goal HbA1c $\leq 6.5\%$, a combination of metformin, a GLP-1 agonist, and another medication such as a thiazolidinedione, sulfonylurea, or meglitinide may be considered.

Clinical recommendations

Based on the review of data from clinical and real-world trials, evidence supports the use of exenatide as a second or third agent when patients are uncontrolled with metformin and/or a sulfonylurea. However, a reduction in the sulfonylurea dose should be considered when initiating exenatide due the risk of hypoglycemia. Consideration should also be given to using exenatide instead of insulin when patients on oral agents need further glycemic control, especially when weight gain or hypoglycemia is particularly undesirable. However, the level of glycemic control should be taken into consideration when choosing therapy as real-world studies have shown exenatide decreasing HbA1c up to –0.9% whereas insulin generally leads to a more pronounced HbA1c reduction.[82] Adding exenatide to thiazolidinedione monotherapy may be considered as it appears to be safe and effective, but additional research is needed to further support this recommendation.

Future Directions

Ongoing clinical trials are investigating the concomitant use of exenatide and insulin, as well as the safety and efficacy of a once-weekly dosage form of exenatide (Table 3). When added to regimens including insulin glargine with or without metformin and/or pioglitazone, patients receiving exenatide had a greater decrease in HbA1c than those receiving placebo (–1.74% vs. –1.04% respectively, $P < 0.001$).[60] The exenatide group experienced significant weight loss (–1.78 kg vs. placebo +0.96 kg, $P < 0.001$) and had a smaller increase in insulin dose, while rates of hypoglycemia were similar.[60]

Currently, exenatide is dosed as a twice-daily injectable, which may be an unfavorable feature for patients and providers. However, a once weekly formulation of exenatide is in development. When administered weekly in doses of 0.8 mg or 2 mg, exenatide weekly decreased HbA1c ranged by –1.0% to –2.0% which was generally statistically significant compared to twice-daily exenatide, placebo, baseline,

or other antidiabetic agents.[61–65] In addition, weight loss with exenatide weekly ranged from −0.04 kg to −4.5 kg.[61,62,64,65] Weight change between exenatide and placebo or twice-daily exenatide was generally, but not always statistically significant with exenatide weekly. One of the five studies reported a weight gain of +0.3 kg with exenatide weekly 0.8 mg and a weight loss of −0.8 kg with exenatide weekly 2 mg, but did not report a *P*-value or confidence interval.[63] However, this study had a small sample size (N = 30) and baseline mean BMI values ranged from 26.1 kg/m^2 to 26.5 kg/m^2 for the treatment groups, which is smaller than the baseline values of 32 kg/m^2 to 36 kg/m^2 in the other studies.

Blood pressure outcomes with exenatide weekly were similar to changes observed with twice-daily ranging from −3.4 mmHg to −6.2 mmHg for SBP and −1.7 mmHg to −2.8 mmHg for DBP.[62,64,65] These changes generally represented a statistically significant reduction from baseline.[62,65]

Conclusion

Exenatide is a GLP-1 agonist that has demonstrated efficacy in reducing HbA1c values, decreasing weight, and decreasing blood pressure in both clinical trials and in real-world settings. Rates of hypoglycemia are generally low, but sulfonylurea doses should be reduced when exenatide is added due to an elevated risk of hypoglycemia. Patients should be warned about nausea and vomiting that may occur during treatment with exenatide, but also told that these effects typically decrease as treatment continues. Given the safety, efficacy, weight, and blood pressure profile of exenatide, as well as pharmacoeconomic data, exenatide should be considered for second-line treatment in patients with type 2 diabetes, particularly when weight gain and hypoglycemia are undesirable.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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