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# Exenatide

USAN

*Treatment of Type 2 Diabetes*
*GLP-1 Receptor Agonist*

Exendin-4
AC-2993
LY-2148568

L-Histidyl-glycyl-L-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-leucyl-L-seryl-L-lysyl-L-glutaminyl-L-methionyl-L-glutamyl-L-glutamyl-L-glutamyl-L-alanyl-L-valyl-L-arginyl-L-leucyl-L-phenylalanyl-L-isoleucyl-L-glutamyl-L-tryptophyl-L-leucyl-L-lysyl-L-asparaginyl-glycyl-glycyl-L-prolyl-L-seryl-L-seryl-glycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide

$C_{184}H_{282}N_{50}O_{60}S$
Mol wt: 4186.608
CAS: 141732-76-5
EN: 271636

**Abstract**

Exenatide is the first in a new class of therapeutic agents known as incretin mimetics. It exhibits glucose-lowering activity similar to the naturally occurring incretin hormone glucagon-like peptide-1 (GLP-1). Exenatide is under development for improving glucose control in patients with type 2 diabetes who are not achieving adequate control through diet and oral medications alone. In rodent models, exenatide has been shown to significantly reduce fasting and postprandial glucose excursions and plasma glucagon levels. A direct effect upon β-cell mass was also demonstrated. Early phase II studies confirmed the antidiabetic effects of exenatide in patients with type 2 diabetes. Clinical studies have included a program of 3 pivotal studies in patients who had not achieved adequate glycemic control with oral antidiabetic agents. The results of these studies have shown that patients treated with exenatide had reduced average glucose levels and improved glycemic control. A New Drug Application (NDA) is planned for mid-2004.

## Introduction

Type 2 diabetes is characterized by a progressive failure of β-cells in the pancreas to produce insulin. An increasing inability to adequately achieve target blood glucose levels through dietary control and using oral medications results in patients moving to control of blood glucose with injectable insulins (1, 2). The naturally occurring incretin hormone glucagon-like peptide-1 (GLP-1) stimulates the body's ability to produce insulin in response to elevated blood glucose levels, inhibits the release of glucagon following meals and slows the rate of nutrient absorption into the bloodstream. The therapeutic potential of GLP-1, however, is limited by its short half-life *in vivo*, and analogues of GLP-1 have therefore been studied (3, 4). Exenatide (synthetic exendin-4, AC-2993), a synthetic form of a peptide originally isolated from Gila monster (*Heloderma suspectum*) venom, shows 53% amino acid homology to GLP-1, but is more stable and longer acting (5). It is the first in a new class of therapeutic agents known as incretin mimetics. It is a potent 39-amino-acid peptide that exhibits glucose-lowering activity and is under development for improving glucose control in patients with type 2 diabetes who do not achieve adequate control through diet and oral medications alone (6).

## Pharmacological Actions

The homeodomain transcription factor PDX-1 (also known as IDX-1, IPF-1 and STF-1) is critical for early development of both the endocrine and exocrine pancreas and is required for islet β-cell development and differentiation. PDX-1 expression is impaired in rodent

J.A. McIntyre, M. Bayés. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

models of diabetes. The effect of exenatide on the expression of PDX-1 was therefore investigated in mouse pancreas, human fetal pancreas cells and intrauterine growth-retarded rats. Following treatment with GLP-1 or exenatide, induction of PDX-1 protein in mouse pancreas and PDX-1 immunofluorescence in exocrine tissue was observed. Islet-like cell clusters derived from human fetal pancreas were treated with exenatide and there was a dramatic increase in the number of cells expressing PDX-1, but no change in insulin expression. In intrauterine growth-retarded rats treated with exenatide during the prediabetic neonatal period, there was a normalization of PDX-1 messenger RNA levels at 14 days, which persisted at 3 months. Treatment with exenatide markedly prevented the development of diabetes seen in adults in this model, which was attributable to its ability to prevent the progressive decrease in insulin-producing β-cell mass (7-9).

The antidiabetic actions of exenatide have been studied in diabetic fatty Zucker (ZDF) rats, a rodent model of type 2 diabetes. Exenatide, 2.6 μg/h, was administered by 30-min i.v. infusion to anesthetized lean or obese rats. A significant decrease in plasma glucagon levels was observed in both lean and obese animals compared to controls administered saline. The suppression of basal glucagon secretion occurred despite significant decreases in plasma glucose in rats treated with exenatide, indicating a mechanism independent of elevations in plasma glucose (10).

In further studies, 7-week-old (prediabetic) ZDF rats were injected once or twice daily with exenatide at a dose of 1 μg or saline for 8 weeks. The increases in fasting plasma glucose, hemoglobin A1c (HbA1c) and fasting total cholesterol were significantly reduced in rats treated with twice-daily exenatide compared with those observed in saline-treated control rats; fasting plasma glucose increased from 137 to 520 mg/dl in control rats, compared with 145 to 250 mg/dl in exenatide-treated rats. Exenatide-treated rats showed no increase in plasma fructosamine levels. There were intermediate increases in all parameters in rats treated with once-daily exenatide. The studies demonstrated that exenatide slowed the progression of diabetes in the ZDF rat model and reduced the associated hypercholesterolemia (11, 12).

The sustained glucose-lowering effect of exenatide has also been demonstrated in *db/db* mice. A prolonged reduction in hyperglycemia of > 25% was maintained for up to 24 h, compared with a loss of effect by 8 h in mice treated with GLP-1. The reduction in hyperglycemia was correlated with increased insulin levels and reduced glucagon levels in the circulation (13, 14). In mice treated with exenatide 24 nmol/kg/day for 13 weeks, HbA1c and blood glucose were significantly lower than in nontreated diabetic animals (15).

Exenatide has been studied in an oral glucose tolerance test in lean C57BL/6J mice. A dose-dependent inhibition of glucose excursions was observed, with a maximum 90% inhibition. The results indicated that exenatide inhibited blood glucose excursions by enhancing the insulin response to a nutrient load and by impairing gastric emptying (16).

The effects of chronic administration of exenatide were investigated in diet-induced obese mice. Exenatide (3, 10 or 30 μg/kg/day) was infused for 28 days to C57BL/6J mice fed a high-fat diet. There was a dose-dependent decrease in average weight gain, body fat content, food intake and plasma glucose in these mice compared with control mice (17). Central and peripheral administration of exenatide has also been shown to reduce food intake in Sprague-Dawley rats (18).

Chronic administration of exenatide was examined in nondiabetic, obese, insulin-resistant Zucker fatty (*fa/fa*) rats, in which plasma glucose was only mildly elevated. Three groups of 9-week-old rats were injected twice daily with exenatide 3 μg/kg or saline for 6 weeks using a pair-fed design. Average daily food consumption and body weight were reduced in the exenatide-treated and pair-fed rats compared with the control group. The increases in HbA1c and total cholesterol observed in these groups were also significantly less than those in the control group. Hyperinsulinemic euglycemic clamp studies performed at the end of treatment showed that animals receiving exenatide had a glucose infusion rate more than double that of the control group (10.31 mg/kg/min *vs.* 4.43 mg/kg/min), whereas that in the pair-fed group was increased by a factor of 1.8. The results of the study demonstrated that the improved insulin sensitivity observed in these insulin-resistant rats was independent of the glycemic improvement induced by restricted nutrient intake (19, 20).

Immunohistochemical analysis showed that after 6 weeks, β-cell mass was significantly higher in rats treated with exenatide 3 μg/kg twice daily than in either control or pair-fed rats. β-Cell mass was positively related to HbA1c and body weight. Exenatide-treated rats showed a relative 50% increase in β-cell mass after adjustment for insulin sensitivity index and these results indicated a direct trophic effect of exenatide to promote islet neogenesis independently of other antidiabetic effects (21).

Other hyperinsulinemic euglycemic clamp studies have demonstrated decreases in glucagon secretion and provided further evidence supporting increased insulin sensitivity in ZDF rats treated with exenatide. The mean plasma glucagon concentration in exenatide-treated rats wwas almost half that in saline-infused rats (165 pM *vs.* 298 pM) and glucose infusion rates were significantly increased (111% in exenatide-treated rats *versus* control rats) (22).

The efficacy of exenatide in lowering HbA1c, fasting plasma glucose and food intake in ZDF rats was demonstrated following both continuous infusion for 28 days, twice-daily injections and a single injection of long-acting release (LAR) exenatide (23, 24). *In vitro* studies had demonstrated a desensitization of the β-cell response following prolonged exposure to exenatide. However, this was not associated with a reduction in β-cell secretory capacity, which would correlate with the observed efficacy of exenatide following prolonged treatment (25).

Further studies in *db/db* mice and rats have demonstrated the potential for administration of exenatide via noninjectable routes such as tracheally, nasally and sublingually (26).

The effect of exenatide administered during the prediabetic period was investigated in Goto-Kakizaki rats, a genetic, nonoverweight model of type 2 diabetes. Rats were injected with exenatide 3 μg/kg/day from postnatal day 2 to day 6. β-Cell mass was measured on day 7 and at 2 months. On day 7, β-cell mass was increased by exenatide-stimulated neogenesis and regeneration compared to Wistar and untreated Goto-Kakizaki rats. The effect upon β-cell mass continued to adulthood, as shown by the assessments at 2 months (27).

A study in a rat partial pancreatectomy model of type 2 diabetes also demonstrated the beneficial effect of exenatide on β-cell growth and differentiation. Following surgery, exenatide 1 nmol/kg/day was administered for 10 days. These rats showed improved glucose tolerance 25 days after surgery compared with controls treated with saline. Morphometric studies showed that there was an increase in β-cell mass. Exenatide therefore appears to stimulate the regeneration of the pancreas by both neogenesis and proliferation of β-cells (28).

### Pharmacokinetics and Metabolism

In a pharmacokinetic study comparing exenatide and GLP-1 in rats, exenatide demonstrated a significantly longer plasma half-life than GLP-1 after i.v., s.c. or i.p. administration. Bolus doses of 0.05, 0.5, 5 and 50 nmol were administered. The estimated half-lives following s.c. administration were 4-7 min for GLP-1 compared with 1.5-3.5 h for exenatide. Increases in maximum concentrations and time-concentration profiles (AUC) were proportional to dose for all routes of administration. The significant differences in clearance rates between exenatide and GLP-1 are likely to correspond to the reported differences in duration of biological action between the two peptides (29).

### Clinical Studies

Exenatide reduced fasting and postprandial glucose levels in healthy volunteers. Eight subjects were infused with exenatide 0.05 pmol/kg/min i.v. or saline in a randomized, double-blind manner. Exenatide significantly reduced fasting plasma glucose levels, although not into the hypoglycemic range. The peak change in postprandial glucose from baseline was also significantly decreased. There was a delay in gastric emptying following a standard test breakfast, and food intake at a free-choice buffet lunch was also decreased by 19% in subjects treated with exenatide. Exenatide infusion had no effect on blood pressure or pulse rate. The study demonstrated that exenatide reduced both fasting glucose levels and postprandial glucose excursions in healthy volunteers, and that this effect appeared to be mediated by a delay in gastric emptying, as well as reduced caloric intake (30). The results of this study and some that follow are summarized in Table I.

The effects of exenatide upon plasma glucose and insulin concentrations were also investigated in 5 groups of healthy volunteers. A total of 40 subjects received 1 of 5 doses of exenatide (0.01-0.3 μg/kg) or placebo, following an overnight fast. Exenatide decreased plasma glucose levels without inducing hypoglycemia and increased plasma insulin levels in a dose-dependent manner (31).

The insulinotropic effect of exenatide was studied in hyperglycemic glucose clamp protocols comparing nondiabetic subjects with type 2 diabetic subjects. Plasma insulin was potentiated 4-5-fold in both groups and remained elevated for 5-6 h after termination of the exenatide infusion, demonstrating its potent and long-lasting effects (32).

The insulinotropic effects of exenatide and its effects on postprandial glycemic excursions were further explored in a number of studies in patients with type 1 and type 2 diabetes. In 13 subjects with type 2 diabetes, single s.c. doses of exenatide of 0.05, 0.1 and 0.2 μg/kg, or placebo, were administered on separate days after an overnight fast. Mean fasting plasma glucose decreased, and mean serum insulin levels increased in a dose-dependent manner. Mean fasting plasma glucose during the 8-h postdose period was 138 and 109 mg/dl for the 0.05 and 0.2 μg/kg doses, respectively, compared to 195 mg/dl for placebo (33). In another study in 8 subjects with type 1 diabetes, exenatide doses of 0.02, 0.04 and 0.08 μg/kg, administered before breakfast, significantly reduced time-averaged AUCs for plasma glucose concentrations compared to placebo (34). Similar studies conducted in subjects with type 1 diabetes with no residual β-cell function and in subjects with a type 1 diabetes mellitus phenotype showed that exenatide reduced glycemic excursions after meals, consistent with a mechanism involving delayed gastric emptying and suppression of glucagon secretion (35, 36).

In 8 diet-treated type 2 diabetic subjects, exenatide was administered twice daily (0.4 $\mu g/m^2$) or 4 times daily (0.2 $\mu g/m^2$) in a placebo-controlled, double-blind, 24-h study, with a standard 4-meal profile. Each subject was studied on 4 occasions with a 1-month washout period between treatments. Treatment with exenatide significantly reduced both mean daytime glucose concentrations and postprandial glucose excursions; treatment effects were similar for both regimens of exenatide (37). In a study of similar design in 7 sulfonylurea-treated type 2 diabetic patients, exenatide had the same effects upon glucose concentrations, and significantly improved basal β-cell function compared with placebo (38).

Exenatide was also investigated in 7 male, non-insulin-using subjects with type 2 diabetes who had discontinued other antidiabetic therapy for a minimum of 7 days. Subjects received exenatide, 0.1, 0.2 or 0.3 μg/kg, under a single-blind, ascending-dose, placebo-controlled, crossover design. Mean peak plasma glucose

*Table I: Clinical studies of exenatide (from Prous Science Integrity®).*

| Indication | Design | Treatments | n | Conclusions | Ref. |
|---|---|---|---|---|---|
| Diabetes mellitus type 2 | Randomized, Double-blind, Crossover | Exenatide, 0.05 pmol/kg/min iv for 285 min sd<br>Placebo | 8 | Compared with placebo, exenatide reduced fasting plasma glucose levels, reduced the peak change of postprandial glucose from baseline and delayed gastric emptying in healthy volunteers. Exenatide was also associated with a lower caloric intake, thus suggesting that it may be especially useful for obese patients with type 2 diabetes | 30 |
| Healthy Volunteers | Randomized, Double-blind | Exenatide, 0.01 μg/kg sc sd<br>Exenatide, 0.05 μg/kg sc sd<br>Exenatide, 0.1 μg/kg sc sd<br>Exenatide, 0.2 μg/kg sc sd<br>Placebo | 40 | In healthy volunteers, subcutaneous exenatide was well tolerated at doses of 0.1 μg/kg or less and dose-dependently increased plasma insulin and reduced plasma glucose levels, without inducing hypoglycemia | 31 |
| Diabetes mellitus type 2 | Open | Exenatide, 0.59 [reduced to 0.15] pmol/kg/min iv over 1 h | 22 | The infusion of exenatide for 60 min increased the plasma insulin response in healthy volunteers and patients with type 2 diabetes after the application of a hyperglycemic clamp. Both hyperglycemia and high insulin levels in plasma were maintained for several hours after exenatide administration | 32 |
| Diabetes mellitus type 2 | Randomized, Double-blind, Crossover | Exenatide, 0.05 μg/kg sc sd<br>Exenatide, 0.1 μg/kg sc sd<br>Exenatide, 0.2 μg/kg sc sd<br>Placebo | 13 | Exenatide dose-dependently increased plasma insulin levels and reduced plasma glucose levels after an overnight fast in patients with type 2 diabetes | 33 |
| Diabetes mellitus type 1 | Randomized, Double-blind, Crossover | Exenatide, 0.02 μg/kg sc sd + Insulin<br>Exenatide, 0.04 μg/kg sc sd + Insulin<br>Exenatide, 0.08 μg/kg sc sd + Insulin<br>Placebo + Insulin | 8 | Subcutaneous exenatide administered with insulin before meals suppressed pancreatic polypeptide (HPP) responses and reduced glycemic excursions in patients with type 1 or 2 diabetes | 34 |
| Diabetes mellitus type 1 | Randomized, Double-blind, Crossover | Exenatide, 0.03 μg/kg sc sd + Insulin<br>Placebo + Insulin | 13 | Exenatide suppressed the abnormal glucagon response and delayed gastric emptying in patients with type 1 diabetes and no β-cell function | 35 |
| Diabetes mellitus | Randomized, Double-blind, Crossover | Exenatide, 0.08 [max] μg/kg sc sd<br>Placebo | 13 | In patients with insulin-treated diabetes, exenatide reduced glycemia through a mechanism that involved delayed gastric emptying and suppression of glucagon secretion | 36 |
| Diabetes mellitus type 2 | Randomized, Double-blind, Crossover | Exenatide, 0.4 μg/m$^2$ sc bid<br>Exenatide, 0.2 μg/m$^2$ sc qid<br>Insulinotropin, 1.2 pmol/kg/min iv over 20 h sd<br>Placebo | 8 | Both subcutaneous exenatide and intravenous insulinotropin significantly reduced the mean plasma glucose levels of patients with type 2 diabetes | 37, 38 |
| Diabetes mellitus type 2 | Crossover | Exenatide, 0.1 μg/kg sc sd<br>Exenatide, 0.2 μg/kg sc sd<br>Exenatide, 0.3 μg/kg sc sd<br>Exenatide, 0.4 μg/kg sc sd<br>Placebo | 7 | Exenatide was well tolerated and dose-dependently reduced the postprandial plasma levels of glucose in patients with type 2 diabetes and dose-dependently increased the feeling of fullness and satiety after challenge with 7 kcal/kg of Sustacal® | 39 |
| Diabetes mellitus type 2 | Randomized, Double-blind, Crossover | Exenatide, 0.01 μg/kg sc sd<br>Exenatide, 0.02 μg/kg sc sd<br>Exenatide, 0.05 μg/kg sc sd<br>Exenatide, 0.1 μg/kg sc sd<br>Placebo | 14 | Exenatide slowed gastric emptying and dose-dependently reduced the postprandial increase in plasma glucagon levels in patients with type 2 diabetes | 40 |

*Continued*

*Table I Cont.: Clinical studies of exenatide (from Prous Science Integrity®).*

| Indication | Design | Treatments | n | Conclusions | Ref. |
|---|---|---|---|---|---|
| Diabetes mellitus type 2 | Randomized, Double-blind, Crossover | Exenatide, 0.1 μg/kg sc bid x 5 d<br>Placebo | 24 | Exenatide slowed gastric emptying and was more effective than placebo in reducing the postprandial levels of glucagon, triglycerides and glucose in the plasma of patients with type 2 diabetes | 41 |
| Diabetes mellitus type 2 | Randomized, Single-blind, Crossover | Exenatide, 0.2, 0.4, 0.6 or 0.8 μg/kg sc<br>Placebo | 12 | Exenatide was well tolerated and dose-dependently decreased plasma glucose levels in patients suffering from type 2 diabetes | 42 |
| Diabetes mellitus type 2 | Randomized, Double-blind | Exenatide, 0.08 μg/kg bid [breakfast and dinner] + Diet + Sulfonylurea and/or Metformin x 28 d (n=26)<br>Exenatide, 0.08 μg/kg bid [breakfast and bedtime] + Diet + Sulfonylurea and/or Metformin x 28 d (n=27)<br>Exenatide, 0.08 μg/kg tid [breakfast, dinner and bedtime] + Diet + Sulfonylurea and/or Metformin x 28 d (n=28)<br>Placebo (n=28) | 109 | The addition of exenatide significantly improved glycemic control in patients with type 2 diabetes who were already receiving sulfonylurea and/or metformin. Exenatide was well tolerated and did not increase body weight or induce significant hypoglycemia | 44 |
| Diabetes mellitus type 2 | Open | Exenatide, 5 μg sc bid [breakfast & dinner] 4 wk → 10 μg sc bid | 77 | Exenatide improved glycemic control in patients with type 2 diabetes failing oral agents | 47 |

concentrations occurred 30-45 min after a standardized meal and returned to below baseline levels within 90-120 min following all exenatide doses. Following placebo administration, glucose levels continued to increase to 90 min and did not return to baseline for up to 6 h. There was detectable exenatide plasma immunoreactivity for up to 15 h postdose. The study did not identify any safety issues with regard to routine hematology and blood chemistry parameters or ECG measurements (39).

The inhibition of glucagon secretion and gastric emptying as a dose-response effect was studied in 14 subjects with type 2 diabetes mellitus following withdrawal of oral therapies for 10-14 days. Exenatide at doses of 0.01, 0.02, 0.05 or 0.1 μg/kg or placebo was administered on separate days following an overnight fast. A standard meal was given immediately after the injection. The meal-associated glucagon increment was decreased by 58%, 50% and 47% with 0.02, 0.05 and 0.1 μg/kg doses of exenatide, respectively. The increases in mean postprandial glucose concentrations were dose-dependently reduced to a maximum 30.5 mg/dl decrement below the fasting glucose concentration with 0.1 μg/kg exenatide. Gastric emptying was slowed by up to 53%. The decreases in glucagon secretion and gastric emptying following exenatide administration were comparable to its glucose-lowering potency (40).

The effects of 5-day dosing with exenatide were studied in 24 patients with type 2 diabetes previously treated by diet, oral therapies or insulin, in a single-blind, placebo-controlled, crossover study. Patients received exenatide at a dose of 0.1 μg/kg b.i.d. A Sustacal® meal was administered on days 1 and 5. Postprandial plasma glucose, glucagon and triglycerides were significantly reduced following exenatide administration, and gastric emptying was slowed (41).

The effect of a continuous s.c. infusion of exenatide on glucose concentrations was studied in 12 patients with type 2 diabetes inadequately controlled with metformin and/or diet. Infusions of 0.2, 0.4, 0.6 or 0.8 μg/kg/day were administered for 23 h in a single-blind, placebo-controlled study. Plasma exenatide concentrations were dose-proportional, with the mean concentration following 0.8 μg/kg/day being 270 pg/ml. The average 23-h plasma glucose concentrations were 161 and 140 mg/dl for the 0.2 and 0.8 μg/kg/day doses, respectively, compared with 200 mg/dl for placebo. The study demonstrated the efficacy of a continuous infusion of exenatide in reducing fasting and postprandial glucose concentrations (42).

Phase II studies demonstrated a dose-dependent increase in nausea and vomiting with doses of exenatide above 0.2 μg/kg (31, 39). Population modeling using data from 4 phase II trials evaluating doses of 0.02-0.4 μg/kg exenatide supported the selection of a fixed dose of 10 μg exenatide for evaluation in phase III studies (43).

A total of 109 patients with type 2 diabetes, receiving treatment with metformin, sulfonylureas or a combination of both, were randomized to receive exenatide 0.08 μg/kg in 1 of 3 regimens for 28 days in a placebo-controlled study. Reductions in mean serum fructosamine, mean HbA1c and mean postprandial plasma glucose concentrations were observed with all the exenatide treatment regimens compared with placebo (44).

Three pivotal phase III studies have been conducted in patients with type 2 diabetes. In each of these studies, patients were randomized to receive exenatide or placebo (2:1). Patients randomized to the active drug received

an initial 5-μg dose s.c. twice a day for 1 month. Patients then received either 5 or 10 μg exenatide b.i.d. for a further 6 months. In the first study, 336 patients who had failed to achieve target blood glucose levels with metformin alone were randomized. There were statistically significant dose-dependent reductions in the primary glucose control endpoint in the exenatide groups. The average HbA1c at entry was 8.2%, which was reduced to 7.3% in subjects who received exenatide 10 μg. Almost half of these patients had reduced their HbA1c levels to 7% or less by the end of the study. Patients who received exenatide also showed statistically significant reductions in body weight. No differences in rates of mild to moderate hypoglycemia were observed between active and placebo groups, and there were no episodes of severe hypoglycemia. Only 4 patients in the exenatide groups withdrew from the study due to nausea (6).

In the second pivotal study, 377 patients who had failed to achieve target blood glucose levels with sulfonylureas alone were randomized. With improved glucose control in patients randomized to receive exenatide, the rate of sulfonylurea-induced hypoglycemia increased. The effects of exenatide on HbA1c were similar to in the first pivotal study, with the greatest improvement observed in patients who received 10 μg exenatide; 41% of these patients reduced their HbA1c levels to 7% or less. Statistically significant reductions in body weight were also observed in patients who received the highest dose of exenatide (45).

In the third pivotal study, 734 patients who had failed to achieve target blood glucose levels using a combination of metformin and sulfonylureas were randomized to receive placebo or exenatide, initially 5 μg s.c. b.i.d. for 1 month, followed by 5 or 10 μg b.i.d., and were then further randomized into 2 groups. Patients in the first group maintained their maximally effective dose of sulfonylurea unless hypoglycemia occurred, at which point it could be reduced. The second group reduced their sulfonylurea dose prior to initiating study medication, and subsequently titrated it to achieve glucose control. There were significant reductions in HbA1c in both groups, but there was a lower incidence of mild to moderate hypoglycemia in the second group. In this study, 34% of patients in the highest dose group reduced their HbA1c levels to 7% or less. The primary glucose control endpoint was met in all 3 pivotal phase III studies (46).

In an open-label study of similar design to the pivotal studies, 155 patients who had not achieved target blood glucose concentrations using metformin, sulfonylureas or a combination of both were enrolled. After the initial 4 weeks of treatment, all patients received exenatide 10 μg for a total treatment period of 1 year. Preliminary results in 105 patients showed a mean reduction in HbA1c of 1.3% after 6 months, with 44% patients having a reduction in their HbA1c levels to 7% or less (6, 47). In all clinical studies, the most frequently reported adverse event has been mild to moderate nausea. A phase II dose-escalation trial showed that a clinically meaningful reduction in nausea could be achieved by a gradual increase in the dose of exenatide (6).

A New Drug Application (NDA) for exenatide is planned for mid-2004. In an independent development program, exenatide LAR, a sustained-release formulation of exenatide, is being developed based on Alkermes' Medisorb® injectable sustained-release drug delivery technology.

## Sources

Amylin Pharmaceuticals, Inc. (US); codeveloped with Eli Lilly and Company (US) and Alkermes, Inc. (US).

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