Exenatide: a New Agent for the Treatment of type 2 Diabetes Mellitus as Adjunctive Therapy

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Exenatide is a new anti-diabetic agent that was approved by the FDA in April, 2005 as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or combination of both, but have not achieved adequate glycemic control. Exenatide, a 39-amino acid peptide amide, is a synthetic analogue of the peptide originally derived from a compound found in the salivary secretion of lizard Heloderma suspectum and is a functional analogue of glucagon-like peptide-1 (GLP-1) in human (Fig. 1). It exerts glycemic control via various glucoregulatory mechanisms including glucose-dependent insulinoctropism, suppression of inappropriately high glucagon level, delayed gastric emptying, and reduction of food intake.

While there are an appreciable number of original research publications characterizing the in vitro activity of exenatide, clinical trials are less abundant. This review compiles the results of recently published clinical trials and considers information included in the prescribing information from the manufacturer. Particular attention is given to the utility and safety of this agent.

Mechanism of Action

Exenatide binds to and stimulates the human pancreatic glucagon-like peptide-1 receptor, a seven-transmembrane G-protein coupled receptor, with equal affinity with GLP-1 as demonstrated by the production of cyclic adenosine monophosphate (cAMP) and, thereby increase of insulin secretion.1-3 The in vivo potency of exenatide has been shown to be much greater than that of GLP-1 due to its resistance to the degradation by dipeptidyl

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peptidase-IV (DPP-IV). While exenatide and GLP-1 appear to share certain glucose-lowering actions, they differ in some respects. For example, GLP-1 suppresses gastric acid secretion whereas exenatide does not. Intraportal GLP-1 infusion triggered firing of the hepatic vagal afferent nerves, while exenatide had no effect on them in the same experiment. Exenatide may therefore exert at least one of its actions through a functionally different receptor, although this putative receptor has not yet been identified.

Exenatide stimulates insulin secretion during hyperglycemia, but not during hypoglycemia. This characteristic way of glycemic control is termed glucose-dependent insulinotropism and contrasts with the action of other insulin secretagogues. Currently available hypoglycemic agents predominantly increase insulin secretion independent of prevailing glucose concentrations and thus have a greater potential to induce hypoglycemia. An in vitro model for mechanism of action of exenatide demonstrated that its hypoglycemic effect was by directly acting on pancreatic islets and resultant enhancement of glucose-stimulated insulin secretion. This effect did not persist once exenatide was removed from the system, suggesting that the peptide may be binding and activating target receptors only while it was present in the perfusate. Furthermore, the insulinotropic action of exenatide rapidly decreased when the glucose level was decreased back to normal range, which was consistent with the glucose-dependence of insulinotropism.

Exenatide reduced circulating glucagon level in both the fasting and postprandial states in humans with type 2 diabetes. In a double-blind, placebo-controlled clinical study with 12 patients with type 2 diabetes, exenatide (0.05-0.2 µg/kg subcutaneous injection) induced marked suppression of fasting plasma glucagon level within the first 3 h, while placebo did not cause any change of it. Postprandial plasma glucagon level was also measured in the same study during 180 min following exenatide treatment (0.1 mg/kg subcutaneous injection) and remained unchanged from baseline throughout the postprandial sampling period (180 min). In contrast, postprandial plasma glucagon level in the placebo group increased from 94.9 pg/ml at baseline to 173.9 pg/ml at 60 min and then decreased slowly to 122.7 pg/ml at 180 min. Given with the well-documented elevations in fasting and postprandial glucagon level in patients with type 2 diabetes and the known activity of glucagon with respect to maintaining hepatic glucose output, it is reasonable to extrapolate that glucagon suppression by exenatide contributed to the overall effect of lowered plasma glucose in both the fasting and postprandial periods.

Many published reports suggest that exenatide may increase β-cell mass in the pancreas of diabetic patients. Abraham et al demonstrated that exenatide stimulated differentiation of islet-derived cells into insulin-producing cells by using Nestin-positive islet-derived progenitor cell model. Tourrel et al also reported that exenatide increased β-cell mass and pancreatic insulin content. However, there have been criticisms that increase of β-cell mass may result from an increase in cell size without cell division (hypertrophy), a reduction in β-cell apoptosis, or combination of both. Therefore, it is not evident whether exenatide induces mitosis of pre-existing β-cell and/or neogenesis from ductal stem cells followed by an increase of β-cell number.

Exenatide appears to slow gastric emptying in humans with type 2 diabetes. Delivery of nutrients from the stomach to the small intestine is a critical contributor to postprandial glucose excursions. Indeed, non-diabetic patients who have undergone gastrectomy exhibit postprandial hyperglycemia in spite of apparently normal β-cell function and fasting euglycemia.
emptying time was compared in a double-blind, placebo-controlled clinical study by using plasma level of acetaminophen as a surrogate marker. Peak plasma level of acetaminophen (82.8 µmole/l) was achieved in 3 h after taking acetaminophen and meal in the placebo group. In contrast, the group treated with 0.1 µg/kg of exenatide did not achieve peak plasma level even until 5 h after taking the acetaminophen and meal. The plasma level kept increasing during the period and the maximum was at the end of the period (5 h) with only 52.3 µmole/l, consistent with slowed gastric emptying. The difference in area under the curve (AUC) of acetaminophen was statistically significant (p<0.0001).

**Pharmacokinetic Parameters**

In placebo-controlled clinical studies with type 2 diabetic patients, plasma exenatide level appeared to exhibit dose-proportional kinetics, reaching peak plasma level between 2 and 3 h after single subcutaneous injection. For the 0.02, 0.05, and 0.1 µg/kg exenatide doses, the C\text{max} values were 45, 109, and 187 pg/ml and the AUC\text{0-5h} values were 9,364, 23,224, and 41,387 pg×min/ml, respectively. Elimination half-life (t\text{1/2}) ranged from 3.3 and 4.0 h, and the time to reach maximum concentration (T\text{max}) were between 2.1 and 2.2 h in the corresponding order. Unlike the values for C\text{max} and AUC, elimination half-life and time to reach maximum concentration were not significantly affected by exenatide dose. Exenatide concentrations were detectable for about 15 h following high doses of 0.2 µg/kg and above. C\text{max} and AUC were significantly different for all pairwise dose comparisons between the treatment arms (p < 0.0001). Mean apparent volume of distribution (V\text{d}) for exenatide was 28.3 liters following a subcutaneous administration. Pharmacokinetic parameters of exenatide after a single subcutaneous injection to type 2 diabetic patients are summarized in Table 1.

Exenatide had bioavailability of 65-76 % for subcutaneous and intraperitoneal administration according to the results of nonclinical study using rat. Bioavailability and clearance data in the experiment were not dose-dependent. Elimination of exenatide primarily occurs via glomerular filtration followed by proteolytic degradation. Although renal filtration is the major route for excretion of exenatide, clearance of the drug was not altered to a clinically significant extent in patients with mild to moderate renal impairment having creatinine clearance of 30-80 ml/min at doses of 5 or 10 µg. However, in patients with end stage renal disease requiring hemodialysis, exenatide clearance was significantly lower than in healthy volunteers (0.9 vs 3.4 liters/h; p ≤ 0.0001). Exenatide is not recommended for use in patients with creatinine clearance of < 30mL/min. Race, obesity, age and sex did not appear to significantly alter the pharmacokinetics of exenatide.

**Drug Interactions**

Since primary route for excretion of exenatide is glomerular filtration and subsequent degradation of peptide bonds, drug interaction issue of the drug is less problematic compared to other drugs that are primarily metabolized by microsomal enzymes such as cytochrome P450. However, the absorption rate and extent of other drugs concomitantly administered with exenatide may be reduced due to slow gastric emptying effect exerted by exenatide injection.

Published research articles for drug interaction of exenatide and other drugs are less abundant. In an open-label clinical study with 21 healthy male subjects, co-administration of exenatide 10 mg twice daily did not change the AUC of digoxin but caused a 17% decrease in plasma C\text{max} (1.40 to 1.16 ng/mL) and delayed the T\text{max} by approximately 2.5 h. In the same study, however, exenatide administration did not cause

<table>
<thead>
<tr>
<th>exenatide dose (0.02-0.1 µg/ml)</th>
<th>C\text{max} (pg/ml)</th>
<th>AUC\text{0-5h} (pg×min/ml)</th>
<th>t\text{1/2} (h)</th>
<th>T\text{max} (h)</th>
<th>V\text{d} (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-187</td>
<td>9364-41387</td>
<td>3.3-4.0</td>
<td>2.1-2.2</td>
<td>28.3</td>
<td></td>
</tr>
</tbody>
</table>
changes in digoxin steady-state pharmacokinetics that would be expected to have clinical sequelae. Therefore, dosage adjustment of digoxin does not appear warranted when patients who are already on the drug start using exenatide.

Subcutaneous injection of exenatide 10 mg twice daily did not alter steady-state C max or AUC of lisinopril in patients with mild to moderate hypertension at lisinopril dose of 5-20 mg/day although time to reach maximum plasma level of lisinopril was delayed by 2 h due to slow gastric emptying effect of exenatide. There were no significant changes noted in the mean systolic and diastolic blood pressure during 24-hour. However, pharmacists should aggressively practice patient counseling regarding the goal for blood pressure management because diabetic patients are prone to various complications of hypertension and therefore need to manage their blood pressure more tightly than non-diabetic hypertensive individuals.

Concomitant administration of subcutaneous 10 mg exenatide twice daily decreased AUC and C max of a single dose of lovastatin 40 mg approximately by 40% and 28%, respectively, and delayed T max of lovastatin approximately by 4 h. However, there was no consistent change of lipid profiles compared to baseline in the type 2 diabetic patients who participated in the 30-week controlled clinical trials and were already receiving HMG CoA reductase inhibitors. This may be due to the combined result of decreased efficacy, caused by less absorption of the lipid-lowering agent, and improved lipid profile exerted by exenatide therapy. Pharmacists should be aware of the significant change of major pharmacokinetic parameters of lovastatin (probably including other statin drugs) because dysregulation of lipid metabolism is prevalent in type 2 diabetic patients and is one of the most important major risk factors for cardiovascular complications in the diabetic population. In fact, 33-53 % of all participants in three pivotal Phase III clinical trials were on at least one lipid-lowering agent.

Like other drugs described above, absorption of acetaminophen was also slowed in healthy volunteers and patients with type 2 diabetes. T max of acetaminophen was 0.6 h when it was administered 1 h before exenatide, compared with T max of 0.9, 4.2, and 3.3 h when the drug was administered simultaneously, 1 h, or 2 h after exenatide in the corresponding order. This reflects the delay in gastric emptying exerted by administration of exenatide. Therefore, exenatide should be used with caution in patients receiving oral medications that require rapid gastrointestinal absorption such as antimigraine drugs or colchicine. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs at least 1 h before exenatide injection. The effect of exenatide on the absorption and effectiveness of oral contraceptives has not been characterized.

Clinical Studies

A total of 1446 patients with type 2 diabetes mellitus have been treated with exenatide in three pivotal Phase III clinical trials of triple-blind, placebo-controlled trials with patients with type 2 diabetes. HbA1C, a primary endpoint, revealed significant reduction at week 30 in all treatment arms in the trials. The summary of the three pivotal Phase III clinical trials is shown in Table 2.

DeFronzo and his associates evaluated the ability of exenatide to improve glycemic control in patients with type 2 diabetes who were unable to achieve glycemic control with maximally effective metformin doses. At week 30, a significant dose-dependent reduction in HbA1C was observed in both exenatide-treated arms compared with placebo (p<0.001). For intent-to-treat subjects with baseline HbA1C>7%, 40% in the 10 mg exenatide arm and 27% in the 5 mg exenatide arm reached an HbA1C ≤ 7% at week 30. Similarly, for the evaluable subjects with baseline HbA1C > 7%, 40% in the 10 µg exenatide arm and 32% in the 5 µg exenatide arm reached an HbA1C ≤ 7% by week 30. These proportions of the population (both for intent-to-treat and for evaluable population) were significantly greater than in the placebo arm (p<0.01 for pairwise comparison). Body weight averaged
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Table 2. Summary of pivotal Phase III clinical trials for the treatment of type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Design</th>
<th>DeFronzo et al</th>
<th>Buse et al</th>
<th>Kendall et al</th>
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<tbody>
<tr>
<td>Subjects (n)</td>
<td>336</td>
<td>377</td>
<td>733</td>
</tr>
<tr>
<td>Participants</td>
<td>patients with type 2 diabetes mellitus</td>
<td>patients with type 2 diabetes mellitus</td>
<td>patients with type 2 diabetes mellitus</td>
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<tr>
<td>Treatment protocol</td>
<td>metformin ≥1,500 mg/day and either a SU and either placebo BID, 5 µg placebo BID, 5 µg exenatide BID, or exenatide BID, or 10 µg exenatide BID</td>
<td>metformin ≥1,500 mg/day and a SU and placebo BID, 5 µg placebo BID, 5 µg exenatide BID, or exenatide BID, or 10 µg exenatide BID</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>HbA1C and safety</td>
<td>HbA1C and safety</td>
<td>HbA1C and safety</td>
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<tr>
<td>Baseline</td>
<td>8.2</td>
<td>8.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Change at week 30</td>
<td>+0.1</td>
<td>-0.5</td>
<td>-0.2</td>
</tr>
<tr>
<td>Proportion achieving</td>
<td>50 µg BID 10 µg BID</td>
<td>50 µg BID 10 µg BID</td>
<td>50 µg BID 10 µg BID</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>99.9</td>
<td>99.1</td>
<td>99.1</td>
</tr>
<tr>
<td>Change at week 30</td>
<td>-0.3</td>
<td>-0.9</td>
<td>-0.9</td>
</tr>
</tbody>
</table>

DB=double-blinded; ITT=intention-to-treat; MC=multi-center; BID=twice daily; SU=sulfonylurea

approximately 100 kg at baseline reduced by 1.6 and 2.8 kg for 5 µg and 10 µg exenatide treatment arms, respectively (p<0.001). This clinical trial demonstrated that exenatide 10 µg twice daily therapy in addition to metformin improved overall hyperglycemia in a group of type 2 diabetes with less-than-optimal glycemic control, with about 40 % of patients able to reach an HbA1C treatment goal of ≤7%. It was also noteworthy that exenatide treatment elicited dose-dependent reduction in body weight.

Second pivotal clinical trial was performed by Buse and his colleagues to evaluate the ability of exenatide to improve glycemic control in patients with type 2 diabetes failing to achieve glycemic control with maximally effective doses of a sulfonylurea as monotherapy.23)

Participants were 22-76 years of age and had type 2 diabetes treated with at least the maximally effective dose of a sulfonylurea as monotherapy for at least 3 months before screening. Maximally effective dose of sulfonylurea was defined 4 mg/day glimepiride, 20 mg/day glyipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide. For intent-to-treat subjects with baseline HbA1C > 7%, 34.2% in the 10 µg exenatide arm and 26.7% in the 5 µg exenatide arm reached an HbA1C ≤7% at week 30. Similarly, for the evaluable subjects with base line HbA1C >7%, 41.3 % in the 10 µg exenatide arm and 32.0% in the 5 µg exenatide arm reached an HbA1C ≤7% by week 30. These proportions of the population (both for intent-to-treat and for evaluable population) were significantly greater than in the placebo arm (p<0.002 for pairwise comparison). Baseline body weight of placebo arm was slightly higher than treatment arms. Subjects in the 5 µg exenatide arm showed weight reduction of 0.9 kg and subjects in the 10 µg exenatide arm showed reduction of 1.6 kg at the end of study, respectively. Subjects in the placebo arm showed 0.6 kg reduction at the end of study as well. However, pairwise comparison revealed that there was a statistically significant difference between exenatide treatment groups and placebo group (p<0.05).

This clinical trial demonstrated that long-term use of exenatide at fixed doses of 5 and 10 mg twice daily appears to have potential for the treatment of patients with type 2 diabetes not adequately controlled with sulfonylurea agents, with 41.3% able to reach and maintain an HbA1C ≤7% in the 10 µg twice daily dose at the end of 30 weeks.

Third pivotal clinical trial was performed by Kendall and his colleagues to evaluate the effect of exenatide in...
hyperglycemic patients with type 2 diabetes unable to achieve glycemic control with combination therapy of metformin and a sulfonylurea. Participants were 22-77 years of age with type 2 diabetes treated with metformin and a sulfonylurea. General inclusion criteria were a screening fasting plasma glucose level <13.3 mmol/l, body mass index 27-45 kg/m², and an HbA1C 7.5-11.0%. The metformin dose was ≥1,500 mg/day, and the sulfonylurea dose was at least the maximally effective dose for 3 months before screening. The definition of maximally effective dose of sulfonylurea was same as defined in Buse and his colleagues' trial. For intent-to-treat subjects with baseline HbA1C > 7%, 30% in the 10 mg exenatide arm and 24% in the 5 mg exenatide arm reached an HbA1C ≤7% at week 30. Similarly, for the evaluable subjects with base line HbA1C > 7%, 33.5% in the 10 µg exenatide arm and 27.4% in the 5 µg exenatide arm reached an HbA1C ≤7% by week 30. These proportions of the population (both for intent-to-treat and for evaluable population) were significantly greater than in the placebo arm (p<0.0001 for pairwise comparison). Baseline body weights of placebo arm and exenatide treatment arms were about 97-99 kg. Subjects in both exenatide treatment arms showed weight reduction of 1.6 kg from baseline compared to reduction of 0.9 kg in placebo arm. (p<0.01). This clinical study demonstrated that exenatide therapy significantly improved glycemic control in patients with type 2 diabetes and was associated with significant sustained weight loss when added to the commonly used combination therapy of metformin and a sulfonylurea. This therapy may offer another potential treatment option when two-drug therapy fails to maintain adequate glycemic control.

### Adverse Events

The adverse events reported during the three pivotal Phase III clinical trials are summarized in Table 3. The most frequent adverse event was nausea, reaching about 40% incidence or more in all three clinical trials. The incidence was even above 50% of all participants in 10 µg exenatide treatment arm in the trial investigated by Buse and his colleagues. Although nausea was generally mild or moderate in intensity, withdrawal rate due to severe nausea was about 2-4% in exenatide treatment arms of all trials. However, withdrawals due to nausea in the placebo arms were zero or less than 1%, clearly indicating that nausea is an adverse effect of exenatide. There was no correlation between duration of nausea and change in body weight. Nausea was reported at a higher incidence during the initial weeks of therapy (week 0-8) and declined thereafter. Therefore, it appears to be important that pharmacists should counsel patients with regard to this gastrointestinal adverse effect of exenatide to prevent unnecessary discontinuation of the drug and to improve patient compliance.

| Table 3. Adverse drug events during the three pivotal Phase III clinical studies |
|---------------------------------|----------------|----------------|----------------|
|                                 | DeFronzo et al (n=336) | Buse et al (n=377) | Kendell et al (n=733) |
|                                 | Pbo (n=123) | 5 µg (n=125) | 10 µg (n=129) | Pbo (n=113) | 5 µg (n=110) | 10 µg (n=113) | Pbo (n=247) | 5 µg (n=245) | 10 µg (n=241) |
| Nausea                          | 23 36 45 7 39 51 21 39 49 |
| Hypoglycemia                    | 5 5 5 14 36 13 19 28 |
| Dizziness                       | 6 9 4 7 15 15 nd nd |
| Feeling jitters                 | nd nd nd 2 12 15 7 9 12 |
| Vomiting                        | 4 11 12 2 10 13 5 15 14 |
| Diarrhea                        | 8 12 16 4 11 9 7 10 17 |
| Headache                        | nd nd nd 7 9 8 5 11 8 |
| URI                             | 11 14 16 nd nd nd 19 11 17 |

nd=not determined; Pbo=placebo; URI=upper respiratory infection
Second most frequent adverse event was hypoglycemia although there was no severe case. The overall incidence of mild to moderate hypoglycemia was approximately 5% in DeFronzo’s clinical trial with type 2 diabetic patients who were on exenatide and metformin.22) There was no withdrawal reported due to severe hypoglycemia in his trial. In contrast, in Buse’s and Kendall’s clinical trials, the incidences of hypoglycemia were 14 and 19% in 5 µg exenatide arm and 36 and 28% in 10 µg exenatide arm, respectively, compared with the very low incidence in placebo arm.22-23) Withdrawal due to hypoglycemia was one case in 5 µg exenatide arm of Buse’s trial. One case of severe hypoglycemia requiring assistance from another individual, but no medical intervention, was also reported in 5 µg exenatide arm of Kendall’s trial. It is reasonable that participants who were taking an insulin secretagogue concomitantly with other anti-diabetic agents showed higher incidence of hypoglycemia. Participants in Buse’s and Kendall’s trials were on a sulfonylurea (insulin secretagogue) while participants in DeFronzo’s trial were not. Although hypoglycemia associated with combination therapy of exenatide and a sulfonylurea was mild or moderate, dose reduction of the sulfonylurea should be warranted to reduce the risk of hypoglycemia.

Generally, exenatide treatment was not associated in all three pivotal Phase III clinical trials with an increased incidence of cardiovascular, hepatic, or renal adverse events.22-24) No changes in plasma lipids, laboratory safety parameters, heart rate, blood pressure, or electrocardiogram were observed between treatment and placebo arms. Twelve subjects had mild to moderate abnormalities in their blood creatinine phosphokinase level in Buse’s trial. However, all changes were transient with no consistent pattern.

Conclusion

Exenatide improves glycemic control in people with type 2 diabetes by various glucoregulatory mechanisms including glucose-dependent insulinotropism, suppression of inappropriately high glucagon level, delayed gastric emptying, and reduction of food intake. Exenatide is not a substitute for insulin and is not indicated for the treatment of diabetic ketoacidosis. In three pivotal Phase III clinical studies, exenatide 5 or 10 µg twice daily demonstrated significant reduction of HbA1C level after 30 weeks treatment in patients with type 2 diabetes who were unable to achieve optimal glycemic control by metformin and/or a sulfonylurea. Patients should be advised that treatment with exenatide may result in nausea, particularly upon initiation of therapy, followed by reduction of appetite and body weight. Exenatide is not studied for combination therapy with other anti-diabetic agents such as thiazolidinediones, D-phenylalanine derivatives, meglitinides, or alpha glucosidase inhibitors. Exenatide is not recommended for use in patients with end stage renal disease or severe renal impairment.

References

8. Henquin J-C. Triggering and amplifying pathways of regula-