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SUMMARY OF KEY ARTICLES

Identifying Challenges With Insulin Therapy and Assessing Treatment Strategies With Pramlintide

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Identifying Challenges With Insulin Therapy and Assessing Treatment Strategies With Pramlintide

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INTRODUCTION

Identifying Challenges With Insulin Therapy and Assessing Treatment Strategies With Pramlintide

By Steven V. Edelman, MD

Evidence-based studies continue to provide insights into the difficult clinical challenges with insulin therapy, as well as the clinical value of adjunctive therapies. There are several common issues when treating patients with insulin, which can lead to frustration for healthcare providers and patients. Weight gain, hypoglycemia, glucose fluctuations, and an inability to control postprandial plasma glucose (PPG) values are just a few of the unresolved challenges providers and patients face when trying to achieve glycemic control with insulin therapy. SYMLIN® (pramlintide acetate) injection is an adjunctive therapy—that is, a complement to mealtime insulin—and may fulfill unmet clinical needs in patients with type 2 and type 1 diabetes. SYMLIN, a synthetic peptide of human amylin (another ß-cell hormone that is deficient in patients with diabetes), is indicated as an adjunct treatment for patients with type 2 or type 1 diabetes who use mealtime insulin and have not achieved glucose control despite optimal insulin therapy (with or without a concurrent sulfonylurea agent and/or metformin in type 2 diabetes). Clinical studies consistently show significant positive results with the addition of SYMLIN to mealtime insulin therapy in terms of helping patients achieve glucose homeostasis (improved A1C, lower postprandial glucose levels, and reduced glucose fluctuations) and reduce their insulin requirements while simultaneously experiencing weight loss.*,†

THE BURGEONING ROLE OF PPG

The gold standard for glycemic control for years has been glycosylated hemoglobin (A1C), which represents only the average blood glucose levels over the past 2 to 3 months. Hirsch and Brownlee postulate that glucose variability, in combination with A1C, may be a more reliable indicator of glycemic control and the risk for complications than is A1C alone.[1] The glucose values of patients without diabetes will typically vary within a very narrow range compared with what is observed in insulin-treated patients. The body of data in the literature suggests that there are deleterious effects associated with glucose variability; however, longer-term outcome studies need to be completed.

Meanwhile, others are further examining current standards by elucidating the relationship between PPG and A1C. Analysis by Monnier et al concludes that PPG directly impacts A1C. In patients with type 2 diabetes, the contribution of PPG to A1C, relative to the contribution of fasting glucose, increases progressively as A1C decreases toward target levels.[2] Monnier's data help to explain that while treatments that target PPG do lower A1C without causing hypoglycemia, they do not lower A1C as much as treatments that do cause hypoglycemia.[2]

Trying to mimic what happens in the normal, nondiabetic state makes physiologic sense. A person with diabetes typically has PPG levels that not only are high (around 200 mg/dL)[3] but also take several hours to return to baseline.[4] This is quite abnormal compared with healthy individuals, who rarely have a PPG level above 140 mg/dL,[4] even after a high-calorie or carbohydrate-dense meal. Research suggests that normalizing PPG, in addition to normalizing fasting plasma glucose, will help achieve long-term glycemic control.[2]

ASSESSING THE RISKS AND BENEFITS OF INSULIN THERAPY

Many patients do not achieve glycemic control with oral antidiabetic agents, and so they must also use insulin. While insulin may help some patients reach target A1C, the risks associated with increasing doses of insulin, such as weight gain and hypoglycemia, may not always outweigh the benefits. For example, the results of the Treating to Target in Type 2 Diabetes (4-T) study showed that adding and increasing the doses of biphasic, prandial, or basal insulin to maximally tolerated doses of metformin and sulfonylurea helped some patients achieve an A1C of 6.5%, but it led to an increase in hypoglycemic events and weight gain.[5] The Action to Control Cardiovascular Risk in

*In a 6-month, open-label clinical trial, insulin-using patients with type 2 (n=166) or type 1 (n=265) diabetes lost, on average, 6 lb.

† SYMLIN is not indicated for the management of obesity.

Introduction (continued)

Diabetes (ACCORD) study showed that treating patients with intensive therapy to achieve a target A1C of <6.0% increased the incidence of all-cause death, hypoglycemia, and weight gain in patients with type 2 diabetes and risk factors for cardiovascular disease (CVD) or previous cardiovascular events.[6]

NEW TREATMENT STRATEGIES WITH PRAMLINTIDE

In an effort to address the unresolved challenges of insulin therapy, investigators have reported on SYMLIN® (pramlintide acetate) injection as an amylin replacement and an adjunct to insulin in patients with type 2 and type 1 diabetes. Karl et al, for example, note that adding pramlintide to mealtime insulin resulted in a reduction in PPG and A1C in patients with type 2 diabetes, as well as a reduction in weight and in insulin requirements.[7]

In a 1-year controlled trial, Hollander et al found that the addition of SYMLIN to the existing mealtime insulin therapy of patients with type 2 diabetes led to an improvement in long-term glycemic control and to a greater proportion of patients achieving glycemic targets, compared with patients using insulin therapy alone. Additionally, this glycemic improvement occurred without weight gain and without an increase in the rate of severe hypoglycemia.[8] Similar results were reported in a controlled study of 651 patients with type 1 diabetes who were taking mealtime insulin. Ratner et al found that mealtime replacement of amylin with SYMLIN as an adjunct to insulin therapy improved long-term glycemic and weight control.[9]

These seven studies, summarized in this *Journal Scan*, point to the challenges of managing hyperglycemia in patients who require insulin therapy—weight gain, hypoglycemia, glycemic variability, and an inability to reach glycemic targets—and indicate that clinicians should consider new treatment strategies to address these unmet needs. The addition of SYMLIN to mealtime insulin may help overcome many unresolved challenges of insulin therapy. The research findings in this *Journal Scan* supplement provide clinicians with information that can bring about positive results in the clinical care of patients with type 2 diabetes who use insulin and patients with type 1 diabetes. ■

Please see the Important Safety Information on page 12 and the accompanying SYMLIN Prescribing Information, including the **Boxed Warning regarding insulin-induced severe hypoglycemia**.

REFERENCES

1. Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard for glycemic control? *J Diabetes Complications*. 2005;19(3):178-181.
2. Monnier L, Lapinski H, Collette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: Variations with increasing levels of HbA_{1C}. *Diabetes Care.* 2003;26(3):881-885.
3. Schrot RJ. Targeting plasma glucose: Preprandial versus postprandial. *Clin Diabetes.* 2004;22(4):169-172.
4. American Diabetes Association. Postprandial blood glucose. *Diabetes Care*. 2001;24(4):775-778.
5. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med.* 2007;357(17):1716-1730.
6. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358:2545-2559.
7. Karl D, Philis-Tsimikas A, Darsow T, et al. Pramlintide as an adjunct to insulin in patients with type 2 diabetes in a clinical practice setting reduced A1C, postprandial glucose excursions, and weight. *Diabetes Technol Ther.* 2007;9(2):191-199.
8. Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: A 1-year randomized controlled trial. *Diabetes Care*. 2003;26(3):784-790.
9. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: A 1-year, randomized controlled trial. *Diabet Med.* 2004;21(11):1204-1212.

WARNING
SYMLIN is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with SYMLIN use occurs, it is seen within 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.

Should Minimal Blood Glucose Variability Become the Gold Standard of Glycemic Control?

Key Point: Along with a reduction in A1C, a reduction in glucose excursions should be a goal of treatment, as they have been shown to accelerate the development of long-term complications of diabetes.

Glycosylated hemoglobin (A1C) has been—and continues to be—the gold standard of glycemic control, with levels ≤7% being the benchmark for reducing the risk for vascular complications. Diabetes Complications and Control Trial (DCCT) investigators questioned these standards by investigating whether aspects of glucose homeostasis, auxiliary to A1C, could affect the development or progression of microvascular complications. In a 1995 report, DCCT investigators concluded that even when A1C levels were comparable for both intensively treated patients and their conventionally treated counterparts, the latter group experienced a markedly higher risk for progression of retinopathy over time.

INVESTIGATORS' HYPOTHESIS OF PHENOMENON

This higher risk for retinopathy may be due to the increased frequency and magnitude of glycemic excursions in conventionally treated patients, who received fewer insulin injections than did patients in the intensive group. The investigators also postulated that the intensity of this glycemic variability would stimulate the reactive oxygen species (ROS) in complications-prone cells. The overproduction of ROS by the mitochondrial electron-transport chain during periods of hyperglycemia-induced oxidative stress is the chief underlying mechanism of glucose-mediated vascular damage.

Quantifying oxidative stress in relation to glycemia has provided added insight into the ways in which acute hyperglycemia affects aspects of physiologic homeostasis. Based on this emerging evidence, Hirsch and Brownlee hypothesize that glucose excursions and mean A1C are more reliable indicators of blood glucose control and risk for long-term complications than is mean AlC alone.

ASSESSING THE QUALITY OF GLYCEMIC CONTROL

The investigators suggest that the results of the cited studies support their hypothesis that both postprandial and daily glucose excursions may be important but underappreciated mechanisms resulting in ROS accumulation, which in turn accelerates micro- and macrovascular disease. Furthermore, the risk for diabetic complications may be misestimated when the prognostic significance of large glycemic variability is overlooked because mean A1C levels are within or near normal range. Thus, there may be benefit in shifting the focus of therapy toward the stabilization of glucose variability in patients with diabetes, even if AlC remains the same. ■

Based on Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard for glycemic control? *J Diabetes Complications*. 2005;19(3):178-181.

Contributions of Fasting and Postprandial Plasma Glucose Increments to the Overall Diurnal Hyperglycemia of Type 2 Diabetic Patients

Key Point: In addition to A1C, PPG is an important measure of glycemic control. It has been shown that the contribution of PPG to A1C, relative to fasting glucose, increases as A1C decreases toward goal.

Although previous studies suggest that postprandial hyperglycemia contributes to approximately 30% to 40% of the total daytime hyperglycemia, its exact contribution to the overall glycemic control of patients with type 2 diabetes remains largely unknown. The discrepancies in the data published previously might be explained by the interference of several factors. To test the specific effect of PPG levels on overall glycemic control, Monnier, Lapinski, and Colette analyzed the diurnal glycemic profiles of patients with type 2 diabetes with different levels of A1C.

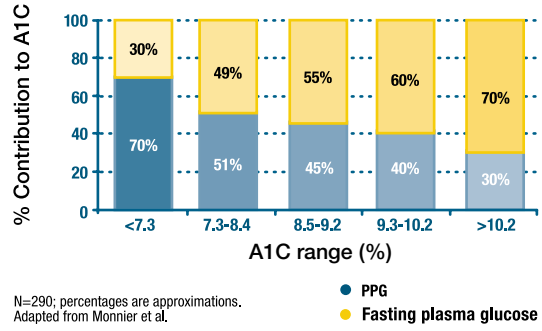
RESEARCH DESIGN AND METHODS

In 290 non–insulin- and non–acarbose-using patients with type 2 diabetes, plasma glucose concentrations were determined at fasting (8:00 AM) and during postprandial and postabsorptive periods (at 11:00 AM, 2:00 PM, and 5:00 PM). The areas under the curve above fasting glucose concentrations (AUC_1) and >109.91 mg/dL (>6.1 mmol/L) (AUC_2) were calculated for further evaluation of the relative contributions of postprandial (AUC_1/AUC_2, %) and fasting ($[AUC_2 - AUC_1]/AUC_2$, %) plasma glucose increments to the overall diurnal hyperglycemia. The data were compared over quintiles of A1C.

RESULTS

As shown in the Figure, the relative contribution of PPG decreased progressively from the lowest (69.7%) to the highest quintile of A1C (30.5%, $P<0.001$). By contrast, the relative contribution of fasting glucose increased gradually with increasing levels of A1C: 30.3% in the lowest to 69.5% in the highest quintile ($P<0.001$).

Figure. Increase in Contribution of Postprandial Plasma Glucose (PPG) as A1C Decreases



N=290; percentages are approximations.
Adapted from Monnier et al.

CONCLUSIONS

According to the investigators, the study results suggest that postprandial glycemic excursions play a major role in the metabolic disequilibrium that is characteristic of patients with mild to moderate hyperglycemia. While fasting hyperglycemia has a large impact on the overall diurnal hyperglycemia experienced by patients with poorly controlled diabetes, PPG elevations play a larger role in glycemic control as patients advance from poorly controlled to controlled diabetes. The importance of postprandial glycemic excursions in patients with fairly well-controlled type 2 diabetes is in agreement with the results of all epidemiological studies. These results are of particular importance when we consider that compared with fasting hyperglycemia, postprandial hyperglycemia has been shown to be a stronger predictor of vascular disease. ■

Based on Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: Variations with increasing levels of HbA_{1C}. *Diabetes Care*. 2003;26(3):881-885.

Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

Key Point: Despite adding increasing doses of mealtime insulin, a minority of patients overall achieved targeted A1C levels, while the majority of patients gained weight and had an increase in hypoglycemic events. Pramlintide was not included in this study.

Type 2 diabetes mellitus is a progressive condition characterized by the continual increase in glucose levels and the dysfunction of beta cells. While the maintenance of nearly normal glycemic levels reduces the risk for diabetic complications, it is difficult to achieve, despite the use of mounting doses of oral antidiabetic agents and the addition of insulin to that regimen. Many patients do not reach targets for glycated hemoglobin (A1C) with this regimen, and there is often great concern regarding the increased risk for hypoglycemia and weight gain. Treating to Target in Type 2 Diabetes (4-T) is a 3-year, multicenter, open-label, randomized, controlled clinical trial that compared the efficacy and safety of adding analogue biphasic, prandial, or basal insulin to the treatment of patients with type 2 diabetes who had suboptimal glycemic control while receiving maximally tolerated doses of metformin and sulfonylurea.

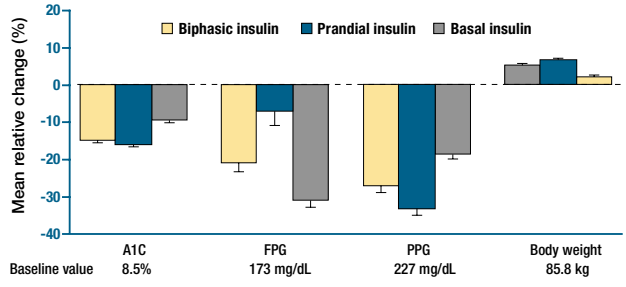
METHODS

The investigators enrolled 708 adults with a suboptimal A1C (7.0% to 10.0%) who were receiving maximally tolerated doses of metformin and sulfonylurea. Patients were randomized to receive twice-daily biphasic insulin aspart, thrice-daily prandial insulin aspart, or once-daily basal insulin detemir (twice if required). The primary outcome measure at 1 year was the mean A1C. Secondary outcome measures included the proportion of patients with an A1C of 6.5% or less, the rate of hypoglycemia, and weight gain.

RESULTS

The maximal reduction in the mean A1C occurred by 24 weeks with the use of escalating doses of insulin and then remained stable. At 52 weeks, the reduction from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 0.8% in the basal group. The respective proportions of patients with an A1C of 6.5% or less were 17.0%, 23.9%, and 8.1%; respective proportions of patients with an A1C of 6.5% or less and without hypoglycemia (grade 2 or more) between weeks 48 and 52 were 52.5%, 43.9%, and 78.9% (P=0.001). Insulin usage continually increased across all groups, and by week 52, patients in the prandial group were using the highest dose. Weight also increased across all groups, with patients in the prandial group experiencing the greatest increase (5.7 kg, 4.7 kg in the biphasic group, and 1.9 kg in the basal group). Mean numbers of hypoglycemic events (grade 2 or more) per patient per year in the biphasic, prandial, and basal groups were 5.7, 12.0, and 2.3, respectively.

Figure. Mean (±SE) Percentage Change From Baseline to 1 Year in A1C, FPG,[a] PPG,[b] and Body Weight



[a] FPG=fasting plasma glucose.
[b] PPG=postprandial plasma glucose.
Adapted from Holman et al.

CONCLUSIONS

Holman and colleagues concluded that a single analogue-insulin formulation added to metformin and sulfonylurea resulted in an A1C of 6.5% or less in a minority of patients at 1 year. Maximal glycemic control appears to happen around week 24. Further reductions were not achieved, despite escalating doses of insulin. Glucose lowering was achieved at the expense of weight gain and an increased risk for hypoglycemia, particularly with the biphasic and prandial regimens. Prandial insulin lowered A1C to the same extent as did biphasic insulin, but with twice the episodes of hypoglycemia and an increase in weight gain of 21%. ■

Based on Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med.* 2007;357(17):1716-1730.

Effects of Intensive Glucose Lowering in Type 2 Diabetes

Key Point: Patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study who received intensive treatment had more hypoglycemia and weight gain than those who received standard treatment. An increase in all-cause mortality among patients in the intensive treatment group was also found. This study suggests that the risks associated with intensive therapy used to lower A1C below standard recommended levels may outweigh the benefits of such treatment. Pramlintide was not included in this study.

The ACCORD trial assessed whether intensive treatment that targets A1C below 6.0% would reduce cardiovascular events more than do treatments that aim to reduce A1C to between 7.0% and 7.9% in patients with type 2 diabetes and either with risk factors for or with established cardiovascular disease (CVD).

METHODS

Patients with type 2 diabetes (mean age, 62.2 years, median A1C of 8.1%) and a history of CVD or risk factors for CVD (35% had a previous cardiovascular event) were randomized to the intensive and standard therapy treatment groups. The primary outcome was the occurrence of nonfatal myocardial infarction (MI), nonfatal stroke, or death from cardiovascular causes. After 3.5 years, the study was discontinued because of the increase in rate of death in the intensive treatment group.

RESULTS

After 4 months with treatment, median A1C had fallen from the baseline median of 8.1% to 6.7% in the intensive treatment group and to 7.5% in the standard treatment group. Median A1Cs of 6.4% and 7.5% were achieved by the intensive and standard treatment groups, respectively, at 1 year and were maintained during follow-up. Patients in the intensive group were exposed to a greater number of treatments and had more frequent changes in the dose or number of treatments.

Compared with the standard treatment group, the intensive treatment group had a significantly higher incidence of hypoglycemia requiring medical assistance (10.5% vs 3.5%, $P<0.001$) and weight gain >10 kg from baseline (27.8% vs 14.1%, $P<0.001$). Also, the rate of nonfatal MI was lower in the intensive group than in the standard group (3.6% vs 4.6%, $P=0.004$), but the rate of death from any cause was higher (5.0% vs 4.0%, $P=0.04$). The rate of death began to separate after 1 year and continued throughout follow-up.

CONCLUSIONS

This study showed that using intensive therapy to target an A1C below 6.0% in patients with type 2 diabetes and risk factors for CVD or previous CVD events resulted in an increase in mortality compared with patients who received standard therapy and who had a targeted A1C between 7.0% and 7.9%. This increase equates to one extra death for every 95 patients who were treated over 3.5 years. The results suggest that the potential benefit (reduction in number of nonfatal MIs) of intensive glucose lowering may not be seen for several years, during which time there is a marked increase in the risk for death from any cause. ■

Based on Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358(24):2545-2559.

Pramlintide as an Adjunct to Insulin in Patients With Type 2 Diabetes in a Clinical Practice Setting Reduced A1C, Postprandial Glucose Excursions, and Weight

Key Point: When taken with mealtime insulin, pramlintide, an analogue of the hormone amylin, reduced A1C and controlled postprandial plasma glucose (PPG) excursions by slowing gastric emptying and regulating food intake, which resulted in weight loss.*,†

The neuroendocrine hormone amylin—deficient in patients with diabetes due to pancreatic ß-cell dysfunction—works in concert with insulin to modulate PPG levels by slowing gastric emptying, suppressing postprandial glucagon secretion, and regulating food intake. Pramlintide is an amylin analogue that, when taken with mealtime insulin in patients with type 2 or type 1 diabetes, has been shown to reduce PPG excursions, A1C, and weight when compared with insulin alone. Karl et al examined the efficacy and safety of pramlintide in patients with type 2 and type 1 diabetes in the clinical practice setting and report the results in patients with type 2 diabetes.

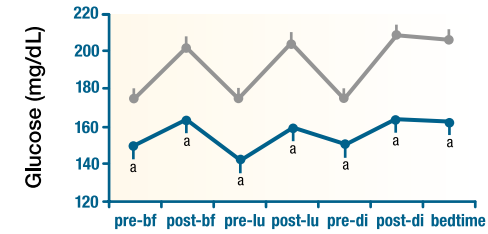
RESEARCH DESIGN AND METHODS

In this uncontrolled, open-label study, 166 patients with type 2 diabetes and a mean A1C of 8.3% added 120 µg of pramlintide to their existing mealtime insulin therapy. At treatment initiation, mealtime insulin doses were reduced 30% to 50% to reduce the risk for hypoglycemia. After pramlintide tolerability was established, doses of basal and mealtime insulin were adjusted, based on the results of self-monitored blood glucose levels, to achieve optimal glucose control. Endpoints included safety, change in A1C, PPG, weight, and insulin doses, as well as responses to a treatment-satisfaction survey given at 6 months.

RESULTS

At 6 months, patients had a significant reduction in A1C (–0.56%, $P<0.05$) and weight (–2.8±0.34 kg, $P<0.05$). A significant reduction in mealtime and basal insulin doses was made during the first 4 weeks of treatment (–21.6% and –12.9%, respectively, $P<0.05$), with results showing a total mean reduction in insulin use of –6.4%±2.66%. After 6 months of treatment, patients reported better overall glucose management, with 80% of patients reporting that taking the extra injections each day was easy or very easy.

Figure. Type 2 Diabetes: Change in Glucose Profile



Open-label clinical trial, pramlintide 120 mcg.
bf, breakfast; lu, lunch; di, dinner;
baseline A1C=8.3%.
[a]$P<0.05$, insulin + pramlintide vs insulin alone;
N=166; data are mean (SE).
Adapted from Karl et al.

Baseline (insulin alone)
6 months (insulin + pramlintide)

Ninety-eight percent of patients reported they would like to continue pramlintide treatment.

Results of seven-point glucose profiles showed that patients taking pramlintide experienced fewer and less severe PPG fluctuations at 6 months than at baseline ($P<0.05$) (Figure).

Karl et al found pramlintide to be generally well tolerated. Overall, 12% of patients experienced hypoglycemia during the 6-month treatment period, with only two patients reporting severe hypoglycemia (0.04±0.02 events per patient-year). Mild-to-moderate nausea was reported by 29.5% of patients receiving a 120-µg dose and was found to be most common during treatment initiation.

CONCLUSION

Despite the use of insulin and oral medications, many patients with diabetes are unable to achieve the desired glucose targets. This study shows that the addition of pramlintide facilitates a reduction in A1C, PPG, and weight while also reducing insulin doses. The reduction in PPG is of particular interest in light of the findings of recent studies suggesting that PPG plays a greater role than fasting glucose in overall glycemic control. ■

*In a 6-month, open-label clinical trial, insulin-using patients with type 2 (n=166) or type 1 (n=265) diabetes lost, on average, 6 lb.

† SYMLIN is not indicated for the management of obesity.

Please see the Important Safety Information on page 12 and the accompanying SYMLIN Prescribing Information, including the **Boxed Warning regarding insulin-induced severe hypoglycemia**.

Based on Karl D, Philis-Tsimikas A, Darsow T, et al. Pramlintide as an adjunct to insulin in patients with type 2 diabetes in a clinical practice setting reduced A1C, postprandial glucose excursions, and weight. *Diabetes Technol Ther*. 2007;9(2):191-199.

Pramlintide as an Adjunct to Insulin Therapy Improves Long-Term Glycemic and Weight Control in Patients With Type 2 Diabetes: A 1-Year Randomized Controlled Trial

Key Point: The addition of pramlintide to insulin therapy has been shown to reduce A1C and weight without increasing the incidence of hypoglycemia.*,†

Despite important advances in insulin therapy, most patients with type 2 diabetes are unable to achieve satisfactory glycemic control. Satisfactory glycemic control with insulin is often intercepted by excessive weight gain, failure to adequately control postprandial glycemic (PPG) excursions, and an increased risk for hypoglycemia. However, the advent of adjunct mealtime amylin replacement with the human amylin analogue pramlintide has been shown to reduce PPG excursions in patients with type 2 diabetes. This study assessed the long-term efficacy and safety of pramlintide in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

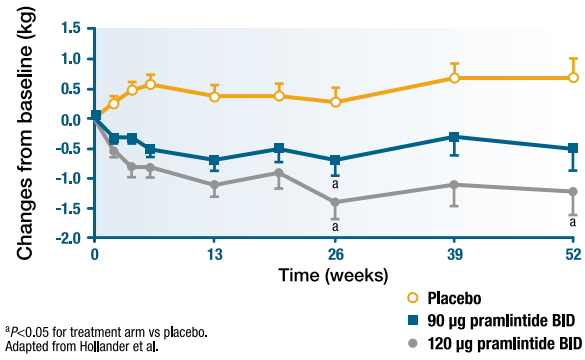
In a 52-week, double-blind, placebo-controlled, parallel-group, multicenter study, 656 patients with type 2 diabetes (age 57±10 years, diabetes duration 12±7 years, body mass index 34.0±7.0 kg/m^2, A1C 9.1%±1.2%, mean±standard deviation) treated with insulin (alone or in combination with sulfonylureas and/or metformin) were randomized to receive additional subcutaneous injections of either placebo or pramlintide (60 µg 3 times a day [TID], 90 µg twice a day [BID], or 120 µg BID).

RESULTS

Hollander et al showed that treatment with pramlintide 120 µg BID led to a sustained reduction from baseline in A1C (–0.68% and –0.62% at 26 and 52 weeks, respectively). This was significantly greater than that in the placebo group ($P<0.05$). In the patients receiving pramlintide in addition to their insulin, an almost twofold greater proportion achieved an A1C <8% (90 µg BID group 42.4% and 120 µg BID 45.7%) compared with the patients receiving placebo plus insulin (27.6%).

Patients in the pramlintide group achieved a greater reduction in weight without increasing body weight. In fact, patients in both pramlintide treatment groups had a significant reduction in body weight by week 26 (both $P<0.05$) (Figure). Patients in the 120 µg BID treatment group sustained this reduction to week 52 ($P<0.05$ vs placebo).

Figure. Change From Baseline in Mean Body Weight



[a]$P<0.05$ for treatment arm vs placebo.
Adapted from Hollander et al.

The greater reductions in A1C in the pramlintide treatment groups were not associated with an overall increase in severe hypoglycemia. Nausea and headache were the only treatment-emergent adverse events that occurred in ≥10% of patients in the pramlintide treatment groups. Nausea was usually mild to moderate and transient. The majority of pramlintide-treated patients did not experience nausea during the study, and only 2% to 4% experienced severe nausea.

CONCLUSIONS

Hollander et al concluded that adding pramlintide to the existing mealtime insulin regimen of patients with type 2 diabetes leads to improved long-term glycemic control. Furthermore, an increased proportion of patients achieved glycemic targets beyond those obtained with insulin therapy alone. Notably, this improvement in A1C was attained without weight gain and without an increase in the overall incidence of severe hypoglycemia. Pramlintide was generally well tolerated, with nausea being mild to moderate and transient. ■

* In a 6-month, open-label clinical trial, insulin-using patients with type 2 (n=166) or type 1 (n=265) diabetes lost, on average, 6 lb.

† SYMLIN is not indicated for the management of obesity.

Please see the Important Safety Information on page 12 and the accompanying SYMLIN Prescribing Information, including the **Boxed Warning regarding insulin-induced severe hypoglycemia**.

Based on Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: A 1-year randomized controlled trial. *Diabetes Care*. 2003;26(3):784-790.

Amylin Replacement With Pramlintide as an Adjunct to Insulin Therapy Improves Long-Term Glycaemic and Weight Control in Type 1 Diabetes Mellitus: A 1-Year, Randomized Controlled Trial

Key Point: Adding pramlintide to insulin therapy reduced A1C and weight without increasing insulin use or the risk for hypoglycemia, and with only mild-to-moderate nausea.*,†

In patients with type 1 diabetes, abnormal autoimmune responses cause the destruction of pancreatic ß cells, resulting in the deficiency of two glucoregulatory peptide hormones, insulin and amylin. Most patients have a very difficult time achieving glycemic goals with insulin replacement alone. In this study, Ratner et al aimed to determine the long-term efficacy and safety of adjunctive therapy with pramlintide, a synthetic human amylin analogue, in patients with type 1 diabetes. By replacing amylin, pramlintide may offer patients with type 1 diabetes improved glycemic control without weight gain.

RESEARCH DESIGN AND METHODS

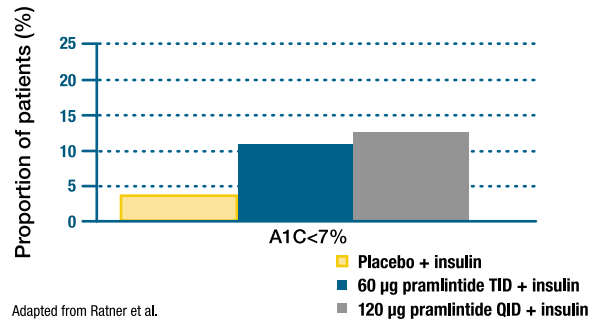
In a double-blind, placebo-controlled, parallel-group, multicenter study, 651 patients with type 1 diabetes (age 41±13 years, A1C 8.9%±1.0%, mean±standard deviation) were randomized to receive mealtime injections of placebo or varying doses of pramlintide, in addition to their insulin therapy, for 52 weeks.

RESULTS

The addition of both 60 µg 3 times a day (TID) and 60 µg 4 times a day (QID) pramlintide to insulin therapy led to significant reductions in A1C from baseline to week 52 (0.29%, P=0.011 and 0.34%, P=0.001, respectively), compared with the placebo group (0.04%) (Figure). Furthermore, three times the proportion of patients in both pramlintide treatment groups achieved an A1C <7%, compared with the placebo group.

Patients in the pramlintide group were able to achieve these A1C reductions without an increase in insulin doses. Patients in the 60 µg TID group decreased insulin use by 3% and patients in the 60 µg QID group decreased insulin use by 6%, compared with patients in the placebo group, who had no change.

Figure. Proportion of Patients Achieving an A1C <7% at Any Time During the Study



Adapted from Ratner et al.

The improvement in A1C with pramlintide was associated with a significant reduction in body weight from baseline to week 52 of 0.4 kg in the 60 µg TID (P<0.027) and QID (P<0.040) pramlintide treatment groups, compared with a 0.8-kg gain in body weight in the placebo group. When data on mean change in weight were stratified by baseline body mass index, results showed not only that pramlintide prevented weight gain in lean patients but also that it induced weight loss in overweight and obese patients.

Mild-to-moderate nausea was the most common adverse event in pramlintide-treated patients. Most nausea was transient and occurred early (within the first 4 weeks) in treatment.

CONCLUSIONS

Ratner et al concluded that for patients with type 1 diabetes taking insulin, replacement of amylin with 60 µg of mealtime pramlintide improves weight and long-term glycemic control via reductions in postprandial glucose. These improvements were achieved without increases in insulin use. ■

* In a 6-month, open-label clinical trial, insulin-using patients with type 2 (n=166) or type 1 (n=265) diabetes lost, on average, 6 lb.

† SYMLIN is not indicated for the management of obesity.

Based on Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: A 1-year, randomized controlled trial. *Diabet Med*. 2004;21(11):1204-1212.

Important Safety Information for SYMLIN® (pramlintide acetate) Injection

WARNING
SYMLIN is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with SYMLIN use occurs, it is seen within 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.

INDICATIONS AND USAGE
SYMLIN is given at mealtimes and is indicated for:

- Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.
- Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.

CONTRAINDICATIONS
Hypersensitivity to SYMLIN or any of its components, including metacresol; confirmed diagnosis of gastroparesis; hypoglycemia unawareness.

WARNINGS
Patient Selection. Proper patient selection is critical to safe and effective use of SYMLIN. SYMLIN therapy should only be considered in patients with insulin-using type 2 or type 1 diabetes who fulfill the following criteria:

- have failed to achieve adequate glycemic control despite individualized insulin management;
- are receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes educator(s).

Patients meeting any of the following criteria should NOT be considered for SYMLIN therapy:

- poor compliance with current insulin regimen;
- poor compliance with prescribed self–blood glucose monitoring;
- have an HbA1c >9%;
- recurrent severe hypoglycemia requiring assistance during the past 6 months;
- presence of hypoglycemia unawareness;
- confirmed diagnosis of gastroparesis;
- require the use of drugs that stimulate gastrointestinal motility;
- pediatric patients.

Hypoglycemia. SYMLIN alone does not cause hypoglycemia. However, SYMLIN is indicated to be co-administered with insulin therapy and in this setting SYMLIN increases the risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. Therefore, when introducing SYMLIN therapy, appropriate precautions need to be taken to avoid increasing the risk for insulin-induced severe hypoglycemia. These precautions include **frequent pre- and post-meal glucose monitoring combined with an initial 50% reduction in pre-meal doses of short-acting insulin.**

ADVERSE EVENTS
The most common adverse event was nausea, which decreased with time in most patients. For adverse events regarding severe hypoglycemia, see WARNINGS.

Please see the accompanying SYMLIN Prescribing Information.

Symlin®
(pramlintide acetate) injection

Medication Guide

SYMLIN® (SĬM-lĭn)
(pramlintide acetate) injection

Read the Medication Guide and the "Patient Instructions for Use" that come with your SYMLIN product before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment.

What is the most important information I should know about SYMLIN?

- **SYMLIN is used with insulin to lower blood sugar, especially high blood sugar that happens after meals.**
- **SYMLIN is given at mealtimes. The use of SYMLIN does not replace your daily insulin but may lower the amount of insulin you need, especially before meals.**
- **Even when SYMLIN is carefully added to your mealtime insulin therapy, your blood sugar may drop too low, especially if you have type 1 diabetes. If this low blood sugar (severe hypoglycemia) happens, it is seen within 3 hours after a SYMLIN injection. Severe low blood sugar makes it hard to think clearly, drive a car, use heavy machinery or do other risky activities where you could hurt yourself or others.**
- **SYMLIN should only be used by people with type 2 and type 1 diabetes who:**
  - already use their insulin as prescribed, but still need better blood sugar control.
  - will follow their doctor's instructions exactly.
  - will follow up with their doctor often.
  - will test their blood sugar levels before and after every meal, and at bedtime.
  - understand how to adjust SYMLIN and insulin doses.

What is SYMLIN?

SYMLIN is an injectable medicine for adults with type 2 and type 1 diabetes to control blood sugar. SYMLIN slows down the movement of food through your stomach. This affects how fast sugar enters your blood after eating. SYMLIN is always used with insulin to help lower blood sugar during the 3 hours after meals.

Who should not use SYMLIN?

Do <u>not</u> use SYMLIN if you:

- cannot tell when your blood sugar is low (hypoglycemia unawareness).
- have a stomach problem called gastroparesis. This is when your stomach does not empty as fast as it should.
- are allergic to SYMLIN or any ingredients in SYMLIN. See the end of this Medication Guide for a complete list of ingredients.

SYMLIN has not been studied in children.

What should I tell my doctor before starting SYMLIN?

Tell your doctor about all of your medical conditions including if you:

- **are pregnant or planning to become pregnant.** It is not known if SYMLIN can harm your unborn baby. You and your doctor will decide how to best control your blood sugar levels during pregnancy.
- **are breastfeeding.** It is not known if SYMLIN passes into your milk and if it can harm your baby. You and your doctor will decide the best way to feed your baby if you are using SYMLIN.

Keep a list of all the medicines you take. Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. SYMLIN can slow down how other medicines pass through your stomach and may affect how much of them get into your body. You may have to change the times you take certain medicines.

How should I use SYMLIN?

- **You must use SYMLIN exactly as prescribed. The amount of SYMLIN you use will depend on whether you have type 2 or type 1 diabetes.** You and your doctor will decide if you can use SYMLIN.
- It is important for you to carefully read, understand and follow the "Patient Instructions for Use" that comes along with this Medication Guide and your SYMLIN.
- **SYMLIN is available in vials and two SymlinPen® pen-injectors. Your doctor will prescribe the type of SYMLIN that is right for you.**
  - If you have been using the SYMLIN vial with an insulin syringe and you are changing to the SymlinPen® pen-injector: **Your doctor will prescribe the SymlinPen® pen-injector that is right for you, tell you how much SYMLIN to inject and when to inject it.**
  - **It is important that you understand how to inject the right SYMLIN dose. Read the "Patient Instructions for Use" carefully BEFORE giving your first dose with the SymlinPen® pen-injector. The SYMLIN in the pen-injector is a different strength than the SYMLIN in the vial.**
- The way you inject SYMLIN is similar to the way you inject insulin. **Inject SYMLIN under the skin (subcutaneously) of your stomach area (abdomen) or upper leg (thigh).** Inject SYMLIN at a site that is more than 2 inches away from your insulin injection. Do not inject SYMLIN and insulin in the same site.
- To help reduce the chances of getting a reaction at the injection site, allow SYMLIN to come to room temperature before injecting.
- Use a new needle for each SYMLIN injection.
- **Never mix SYMLIN and insulin.** Insulin can affect SYMLIN when the two are mixed together.
- Do <u>not</u> use SYMLIN if the liquid looks cloudy.
- If you take more than your prescribed dose of SYMLIN, you may get nauseous or vomit, and you may not be able to eat the amount of food you usually eat. If you take more SYMLIN than your prescribed dose, pay careful attention to the amount of insulin you use because you may be at more risk for low blood sugar. Contact your doctor for guidance.
- If you miss or forget a dose of SYMLIN, wait until the next meal and take your usual dose of SYMLIN at that meal. <u>Do not take more than your usual dose of SYMLIN</u>.

Using SYMLIN and insulin with Type 2 Diabetes

1. Start SYMLIN at 60 mcg injected under your skin, just before major meals. A major meal must have at least 250 calories or 30 grams of carbohydrate.
2. Reduce your rapid-acting or short-acting insulin, including fixed-mix insulin such as 70/30, used before meals by **50 percent**. This means half of the dose you usually use.
3. You must check your blood sugar before and after every meal and at bedtime.
4. Increase your dose of SYMLIN to 120 mcg on your doctor's instructions if you have not had any nausea for 3 days or more.
5. Tell your doctor right away if you have nausea with the 120 mcg dose. Your doctor will tell you how to adjust your dose of SYMLIN.
6. Your doctor may make changes to your insulin doses to better control your blood sugar once you are using the 120 mcg dose of SYMLIN. All insulin changes should be directed by your doctor.

Using SYMLIN and insulin with Type 1 Diabetes

1. Start SYMLIN at 15 mcg injected under your skin, just before major meals. A major meal must have at least 250 calories or 30 grams of carbohydrate.
2. When starting SYMLIN, reduce your rapid-acting or short-acting insulin, including fixed-mix insulin such as 70/30, used before meals by **50 percent**. This means half of the dose you usually use. All insulin changes should be directed by your doctor.
3. You must check your blood sugar before and after every meal and at bedtime.
4. Increase your dose of SYMLIN to 30 mcg on your doctor's instructions if you have not had any nausea for 3 days or more. If you have nausea with SYMLIN at 30 mcg, call your doctor right away. Your doctor may decide that you should stop SYMLIN.
5. Increase your dose of SYMLIN to 45 mcg on your doctor's instructions if you have not had any nausea for 3 days or more while using the 30 mcg dose.

6. Increase your dose of SYMLIN to 60 mcg on your doctor's instructions if you have not had any nausea for 3 days or more while using the 45 mcg dose.
7. Call your doctor right away if you are bothered with nausea on the 45 mcg or 60 mcg dose. Your doctor may decide that you should reduce SYMLIN to the 30 mcg dose.
8. Your doctor may make changes to your insulin doses to better control your blood sugar once you are on a dose of SYMLIN that is right for you. All insulin changes should be directed by your doctor.

Staying on SYMLIN

- Once you reach your recommended dose of SYMLIN, talk to your doctor about changing your insulin doses to better control your blood sugar. You may have to increase your long-acting insulin to prevent high blood sugar (hyperglycemia) between meals. **Insulin changes should always be directed by your doctor based on blood sugar testing.**
- Call your doctor if nausea or low blood sugar continues while on your recommended dose of SYMLIN. Low blood sugar that happens often is a warning sign of possible severe low blood sugar, especially if you have type 1 diabetes.
- **If you stop taking SYMLIN for any reason, such as surgery or illness, talk to your doctor about how to re-start SYMLIN.**

When should I not use SYMLIN?

Do not use SYMLIN if:

- your blood sugar is too low.
- you do not plan to eat. Do not inject SYMLIN if you skip a meal.
- you plan to eat a meal with less than 250 calories or 30 grams of carbohydrate.
- you are sick and can't eat your usual meal.
- you are having surgery or a medical test where you cannot eat.
- you are pregnant or breastfeeding and have not talked to your doctor.

Talk to your doctor if you have any of these conditions.

What should I avoid while taking SYMLIN?

- Do not drive or operate dangerous machinery until you know how SYMLIN affects your blood sugar. Low blood sugar makes it hard to think clearly, drive a car, use heavy machinery or do other risky activities where you could hurt yourself or others. Discuss with your doctor what activities you should avoid.
- Alcohol may increase the risk of low blood sugar.
- **Your doctor will tell you which medicines you can take while using SYMLIN. Do not take other medicines that slow stomach emptying.**

What are the possible side effects of SYMLIN?

Low blood sugar (hypoglycemia)

- **SYMLIN is used with insulin to lower your blood sugar, but your blood sugar may drop too low, especially if you have type 1 diabetes.** See "What is the most important information I should know about SYMLIN?"
- When starting SYMLIN, reduce your doses of insulin before meals as recommended by your doctor to reduce the chance of low blood sugar. You and your doctor should talk about a plan to treat low blood sugar. You should have fast-acting sugar (such as hard candy, glucose tablets, juice) or glucagon with you at all times. Call your doctor if you have low blood sugar more often than normal or severe low blood sugar.

  Your chance for low blood sugar is higher if you:

  - do not reduce your insulin dose before meals at the beginning of SYMLIN treatment, as directed by your doctor.
  - use more SYMLIN or insulin than prescribed by your doctor.
  - change your insulin dose without checking your blood sugar.
  - eat less food than your usual meal.
  - are sick and cannot eat.
  - are more active than usual.
  - have a low blood sugar level before eating.
  - drink alcohol.

Always have fast-acting sugar (such as hard candy, glucose tablets, juice) or glucagon available to treat low blood sugar.

Nausea: Nausea is the most common side effect with SYMLIN. Mild nausea is more likely during the first weeks after starting SYMLIN and usually does not last long. It is very important to start SYMLIN at a low dose and increase it as directed by your doctor. See "How should I use SYMLIN?" If nausea continues or bothers you, call your doctor right away.

Other Side Effects: SYMLIN also may cause the following side effects: decreased appetite, vomiting, stomach pain, tiredness, dizziness, or indigestion.

SYMLIN also can cause reactions at the injection site including redness, minor bruising, or pain. See the detailed "Patient Instructions for Use." Follow the directions under "How should I use SYMLIN?" to reduce the chance of an injection site reaction.

Tell your doctor if you have any side effects that bother you or that do not go away.

These are not all the side effects with SYMLIN. Ask your doctor or pharmacist for more information.

How should I store SYMLIN?

- Store SYMLIN that has not been opened in the refrigerator, between 36˚F to 46˚F (2˚C to 8˚C), until you are ready to use it. Protect SYMLIN from light.
- After a vial or pen-injector has been used for the first time, it can be refrigerated or kept at a temperature up to 86˚F (30˚C) for 30 days. Do not leave **above** 86˚F (30˚C). Any vial or pen-injector in use should be thrown away after 30 days, even if it still has medicine in it.
- Unused SYMLIN (opened or unopened) should not be used after the expiration (EXP) date printed on the carton and the label.
- **Do not freeze SYMLIN. Do not use SYMLIN if it has been frozen.**

Keep SYMLIN and all medicines out of the reach of children.

General information about the safe and effective use of SYMLIN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SYMLIN for a condition for which it was not prescribed. Do not give SYMLIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about SYMLIN. Also see the "Patient Instructions for Use" on using the SymlinPen® pen-injector or vial. You can ask your doctor for more about SYMLIN, including information that is written for doctors.

More information on SYMLIN can be found at http://www.SYMLIN.com.

SYMLIN Customer Service is available 24 hours a day at 1-800-349-8919.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

What are the ingredients in SYMLIN?

Active ingredient: pramlintide acetate

Inactive ingredients: metacresol, D-mannitol, acetic acid, and sodium acetate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Literature Revised July 2008

Manufactured for Amylin Pharmaceuticals, Inc.

San Diego CA 92121, USA

1-800-349-8919

http://www.SYMLIN.com

01-05-1233-F; 813006-FF

AMYLIN®

Symlin®
(pramlintide acetate) injection

PRESCRIBING INFORMATION

Rx only

WARNING
SYMLIN is used with insulin and has been associated with an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe hypoglycemia associated with SYMLIN use occurs, it is seen within 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Appropriate patient selection, careful patient instruction, and insulin dose adjustments are critical elements for reducing this risk.

DESCRIPTION

SYMLIN® (pramlintide acetate) injection is an antihyperglycemic drug for use in patients with diabetes treated with insulin. Pramlintide is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic beta cells that contributes to glucose control during the postprandial period. Pramlintide is provided as an acetate salt of the synthetic 37-amino acid polypeptide, which differs in amino acid sequence from human amylin by replacement with proline at positions 25 (alanine), 28 (serine), and 29 (serine).

The structural formula of pramlintide acetate is as shown:

Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NH_2
acetate (salt) with a disulfide bridge between the two Cys residues.

Pramlintide acetate is a white powder that has a molecular formula of $C_{171}H_{267}N_{51}O_{53}S_2 \cdot x\ C_2H_4O_2$ ($3 \leq x \leq 8$); the molecular weight is 3949.4. Pramlintide acetate is soluble in water.

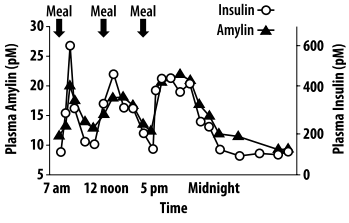
SYMLIN is formulated as a clear, isotonic, sterile solution for subcutaneous (SC) administration. The disposable multidose SymlinPen® pen-injector contains 1000 mcg/mL of pramlintide (as acetate); SYMLIN vials contain 600 mcg/mL of pramlintide (as acetate). Both formulations contain 2.25 mg/mL of metacresol as a preservative, D-mannitol as a tonicity modifier, and acetic acid and sodium acetate as pH modifiers. SYMLIN has a pH of approximately 4.0.

CLINICAL PHARMACOLOGY

Amylin Physiology

Amylin is co-located with insulin in secretory granules and co-secreted with insulin by pancreatic beta cells in response to food intake. Amylin and insulin show similar fasting and postprandial patterns in healthy individuals **(Figure 1)**.

Figure 1: Secretion Profile of Amylin and Insulin in Healthy Adults



Amylin affects the rate of postprandial glucose appearance through a variety of mechanisms. Amylin slows gastric emptying (i.e., the rate at which food is released from the stomach to the small intestine) without altering the overall absorption of nutrients. In addition, amylin suppresses glucagon secretion (not normalized by insulin alone), which leads to suppression of endogenous glucose output from the liver. Amylin also regulates food intake due to centrally-mediated modulation of appetite.

In patients with insulin-using type 2 or type 1 diabetes, the pancreatic beta cells are dysfunctional or damaged, resulting in reduced secretion of both insulin and amylin in response to food.

Mechanism of Action

SYMLIN, by acting as an amylinomimetic agent, has the following effects: 1) modulation of gastric emptying; 2) prevention of the postprandial rise in plasma glucagon; and 3) satiety leading to decreased caloric intake and potential weight loss.

Gastric Emptying. The gastric-emptying rate is an important determinant of the postprandial rise in plasma glucose. SYMLIN slows the rate at which food is released from the stomach to the small intestine following a meal and, thus, it reduces the initial postprandial increase in plasma glucose. This effect lasts for approximately 3 hours following SYMLIN administration. SYMLIN does not alter the net absorption of ingested carbohydrate or other nutrients.

Postprandial Glucagon Secretion. In patients with diabetes, glucagon concentrations are abnormally elevated during the postprandial period, contributing to hyperglycemia. SYMLIN has been shown to decrease postprandial glucagon concentrations in insulin-using patients with diabetes.

Satiety. SYMLIN administered prior to a meal has been shown to reduce total caloric intake. This effect appears to be independent of the nausea that can accompany SYMLIN treatment.

Pharmacokinetics

Absorption. The absolute bioavailability of a single SC dose of SYMLIN is approximately 30 to 40%. Subcutaneous administration of different doses of SYMLIN into the abdominal area or thigh of healthy subjects resulted in dose-proportionate maximum plasma concentrations (C_{max}) and overall exposure (expressed as area under the plasma concentration curve or (AUC)) **(Table 1)**.

Table 1: Mean Pharmacokinetic Parameters Following Administration of Single SC Doses of SYMLIN

SC Dose (mcg)	$AUC_{(0-\infty)}$ (pmol*min/L)	C_{max} (pmol/L)	T_{max} (min)	Elimination $t_{½}$ (min)
30	3750	39	21	55
60	6778	79	20	49
90	8507	102	19	51
120	11970	147	21	48

Injection of SYMLIN into the arm showed higher exposure with greater variability, compared with exposure after injection of SYMLIN into the abdominal area or thigh.

There was no strong correlation between the degree of adiposity as assessed by BMI or skin fold thickness measurements and relative bioavailability. Injections administered with 6.0-mm and 12.7-mm needles yielded similar bioavailability.

Distribution. SYMLIN does not extensively bind to blood cells or albumin (approximately 40% of the drug is unbound in plasma), and thus SYMLIN's pharmacokinetics should be insensitive to changes in binding sites.

Metabolism and Elimination. In healthy subjects, the half-life of SYMLIN is approximately 48 minutes. SYMLIN is metabolized primarily by the kidneys. Des-lys[1] pramlintide (2-37 pramlintide), the primary metabolite, has a similar half-life and is biologically active both *in vitro* and *in vivo* in rats. AUC values are relatively constant with repeat dosing, indicating no bioaccumulation.

Special Populations.

Renal Insufficiency: Patients with moderate or severe renal impairment (Cl_{cr} >20 to ≤50 mL/min) did not show increased SYMLIN exposure or reduced SYMLIN clearance, compared to subjects with normal renal function. No studies have been done in dialysis patients.

Hepatic Insufficiency: Pharmacokinetic studies have not been conducted in patients with hepatic insufficiency. However, based on the large degree of renal metabolism (see Metabolism and Elimination), hepatic dysfunction is not expected to affect blood concentrations of SYMLIN.

Geriatric: Pharmacokinetic studies have not been conducted in the geriatric population. SYMLIN should only be used in patients known to fully understand and adhere to proper insulin adjustments and glucose monitoring. No consistent age-related differences in the activity of SYMLIN have been observed in the geriatric population (n=539 for patients 65 years of age or older in the clinical trials).

Pediatric: SYMLIN has not been evaluated in the pediatric population.

Gender: No study has been conducted to evaluate possible gender effects on SYMLIN pharmacokinetics. However, no consistent gender-related differences in the activity of SYMLIN have been observed in the clinical trials (n=2799 for male and n=2085 for female).

Race/Ethnicity: No study has been conducted to evaluate the effect of ethnicity on SYMLIN pharmacokinetics. However, no consistent differences in the activity of SYMLIN have been observed among patients of differing race/ethnicity in the clinical trials (n=4257 for white, n=229 for black, n=337 for Hispanic, and n=61 for other ethnic origins).

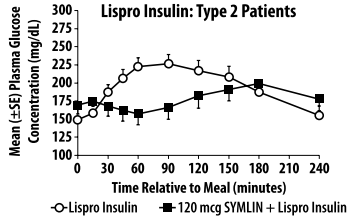
Drug Interactions: The effect of SYMLIN (120 mcg) on acetaminophen (1000 mg) pharmacokinetics as a marker of gastric-emptying was evaluated in patients with type 2 diabetes (n=24). SYMLIN did not significantly alter the AUC of acetaminophen. However, SYMLIN decreased acetaminophen C_{max} (about 29% with simultaneous co-administration) and increased the time to maximum plasma concentration or t_{max} (ranging from 48 to 72 minutes) dependent on the time of acetaminophen administration relative to SYMLIN injection. SYMLIN did not significantly affect acetaminophen t_{max} when acetaminophen was administered 1 to 2 hours before SYMLIN injection. However, the t_{max} of acetaminophen was significantly increased when acetaminophen was administered simultaneously with or up to 2 hours following SYMLIN injection (see PRECAUTIONS, Drug Interactions).

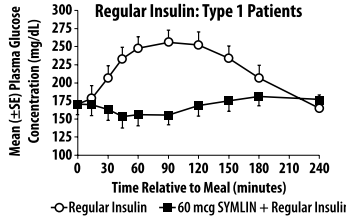
Pharmacodynamics

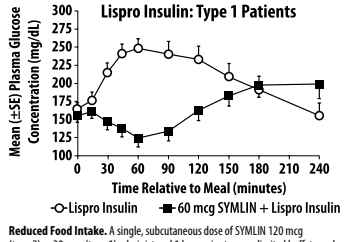
In clinical studies in patients with insulin-using type 2 and type 1 diabetes, SYMLIN administration resulted in a reduction in mean postprandial glucose concentrations, reduced glucose fluctuations, and reduced food intake. SYMLIN doses differ for insulin-using type 2 and type 1 patients (see DOSAGE AND ADMINISTRATION).

Reduction in Postprandial Glucose Concentrations. SYMLIN administered subcutaneously immediately prior to a meal reduced plasma glucose concentrations following the meal when used with regular insulin or rapid-acting insulin analogs **(Figure 2)**. **This reduction in postprandial glucose decreased the amount of short-acting insulin required and limited glucose fluctuations based upon 24-hour glucose monitoring.** When rapid-acting analog insulins were used, plasma glucose concentrations tended to rise during the interval between 150 minutes following SYMLIN injection and the next meal (see DOSAGE and ADMINISTRATION).

Figure 2: Postprandial Plasma Glucose Profiles in Patients With Type 2 and Type 1 Diabetes Receiving SYMLIN and/or Insulin







Reduced Food Intake. A single, subcutaneous dose of SYMLIN 120 mcg (type 2) or 30 mcg (type 1) administered 1 hour prior to an unlimited buffet meal was associated with reductions in total caloric intake (placebo-subtracted mean changes of ~23% and 21%, respectively), which occurred without decreases in meal duration.

CLINICAL STUDIES

A total of 5325 patients and healthy volunteers received SYMLIN in clinical studies. This includes 1688 with type 2 diabetes and 2375 with type 1 diabetes in short- and long-term controlled clinical trials, long-term uncontrolled clinical trials, and an open-label study in the clinical practice setting.

Clinical Studies in Type 2 Diabetes

The efficacy of a range of SYMLIN doses was evaluated in several placebo-controlled and open-label clinical trials in insulin-using patients with type 2 diabetes. Based on results obtained in these studies, the recommended dose of SYMLIN for patients with insulin-using type 2 diabetes is 120 mcg administered immediately prior to major meals.

Two, long-term (26 to 52 week), randomized, double-blind, placebo-controlled studies of SYMLIN were conducted in patients with type 2 diabetes using fixed dose insulin to isolate the SYMLIN effect. Demographic and baseline characteristics for the 871 SYMLIN-treated patients are as follows: mean baseline HbA1c ranged from 9.0 to 9.4%, mean age was 56.4 to 59.1 years, mean duration of diabetes ranged from 11.5 to 14.4 years, and mean BMI ranged from 30.1 to 34.4 kg/m^2. In both of these studies, SYMLIN or placebo was added to the participants' existing diabetes therapies, which included insulin with or without a sulfonylurea agent and/or metformin.

Table 2 summarizes the composite results across both studies for patients assigned to the 120-mcg dose after 6 months of treatment.

Table 2: Mean (SE) Change in HbA1c, Weight, and Insulin at 6 Months in the Double-Blind, Placebo-Controlled Studies in Patients With Insulin-Using Type 2 Diabetes

Variable	Placebo	SYMLIN (120 mcg)
Baseline HbA1c (%)	9.3 (0.08)	9.1 (0.06)
Change in HbA1c at 6 Months Relative to Baseline (%)	-0.17 (0.07)	-0.57 (0.06)*
Placebo-Subtracted HbA1c Change at 6 Months (%)	NA	-0.40 (0.09)*
Baseline Weight (kg)	91.3 (1.2)	92.5 (1.2)
Change in Weight at 6 Months Relative to Baseline (kg)	+0.2 (0.2)	-1.5 (0.2)*
Placebo-Subtracted Weight Change at 6 Months (kg)	NA	-1.7 (0.3)*
Percent Change in Insulin Doses at 6 Months: Rapid/Short-Acting	+6.5 (2.7)	-3.0 (1.6)*
Percent Change in Insulin Doses at 6 Months: Long-Acting	+5.2 (1.4)	-0.2 (1.3)*

* Statistically significant reduction compared with placebo (p-value < 0.05).

In a cohort of 145 patients who completed two years of SYMLIN treatment the baseline-subtracted HbA1c and weight reductions were: -0.40% and -0.36 kg, respectively.

Open-Label Study in the Clinical Practice Setting. An open-label study of SYMLIN was conducted at the recommended dose of 120 mcg in 166 patients with insulin-using type 2 diabetes who were unable to achieve glycemic targets using insulin alone. A flexible-dose insulin regimen was employed in these patients (see DOSAGE and ADMINISTRATION). In this study, patients adjusted their insulin regimen based on pre- and post-meal glucose monitoring. At baseline, mean HbA1c was 8.3%, mean age was 54.4 years, mean duration of diabetes was 13.3 years, and mean BMI was 38.6 kg/m^2. SYMLIN was administered with major meals. SYMLIN plus insulin treatment for 6 months resulted in a baseline-subtracted mean HbA1c reduction of -0.56 ± 0.15% and a baseline-subtracted mean weight reduction of -2.76 ± 0.34 kg. These changes were accomplished with reductions in doses of total, short-acting, and long-acting insulin (-6.4 ± 2.66, -10.3 ± 4.84, and -4.20 ± 2.42%, respectively).

Clinical Studies in Type 1 Diabetes

The efficacy of a range of SYMLIN doses was evaluated in several placebo-controlled and open-label clinical trials conducted in patients with type 1 diabetes. Based on results obtained in these studies, the recommended dose of SYMLIN for patients with type 1 diabetes is 30 mcg or 60 mcg administered immediately prior to major meals.

Three, long-term (26 to 52 week), randomized, double-blind, placebo-controlled studies of SYMLIN were conducted in patients with type 1 diabetes (N=1717). Two of these studies allowed only minimal insulin adjustments in order to isolate the SYMLIN effect; in the third study, insulin adjustments were made according to standard medical practice. Demographic and baseline characteristics for the 1179 SYMLIN-treated patients were as follows: mean baseline HbA1c range was 8.7 to 9.0%, mean age range was 37.3 to 41.9 years, mean duration of diabetes range was 15.5 to 19.2 years, and mean BMI range was 25.0 to 26.8 kg/m^2. SYMLIN or placebo was added to existing insulin therapies.

Table 3 summarizes the composite results across these studies for patients assigned to the 30 or 60 mcg dose after 6 months of treatment.

Table 3: Mean (SE) Change in HbA1c, Weight, and Insulin at 6 Months in the Double-Blind, Placebo-Controlled Studies in Patients With Type 1 Diabetes

Variable	Placebo	SYMLIN (30 or 60 mcg)
Baseline HbA1c (%)	9.0 (0.06)	8.9 (0.04)
Change in HbA1c at 6 Months Relative to Baseline (%)	-0.10 (0.05)	-0.43 (0.04)*
Placebo-Subtracted HbA1c Change at 6 Months (%)	NA	-0.33 (0.06)*
Baseline Weight (kg)	75.1 (0.6)	76.1 (0.5)
Change in Weight at 6 Months Relative to Baseline (kg)	+0.6 (0.1)	-1.1 (0.1)*
Placebo-Subtracted Weight Change at 6 Months (kg)	NA	-1.7 (0.1)*
Percent Change in Insulin Doses at 6 Months: Rapid/Short-Acting	+1.7 (3.3)	-3.6 (2.9)
Percent Change in Insulin Doses at 6 Months: Long-Acting	+2.5 (1.9)	+1.9 (1.3)

* Statistically significant reduction compared with placebo (p-value < 0.05).

In a cohort of 73 patients who completed two years of SYMLIN treatment the baseline-subtracted HbA1c and weight changes were: -0.35% and 0.60 kg, respectively.

SYMLIN Dose-Titration Trial. A dose-titration study of SYMLIN was conducted in patients with type 1 diabetes. Patients with relatively good baseline glycemic control (mean HbA1c = 8.1%) were randomized to receive either insulin plus placebo or insulin plus SYMLIN. Other baseline and demographics characteristics were: mean age of 41 years, mean duration of diabetes of 20 years, mean BMI of 28 kg/m^2. SYMLIN was initiated at a dose of 15 mcg and titrated upward at weekly intervals by 15-mcg increments to doses of 30 mcg or 60 mcg, based on whether patients experienced nausea. Once a tolerated dose of either 30 mcg or 60 mcg was reached, the SYMLIN dose was maintained for the remainder of the study (SYMLIN was administered before major meals). During SYMLIN titration, the insulin dose (mostly the short/rapid-acting insulin) was reduced by 30-50% in order to reduce the occurrence of hypoglycemia. Once a tolerated SYMLIN dose was reached, insulin dose adjustments were made according to standard clinical practice, based on pre- and post-meal blood glucose monitoring. By 6 months of treatment, patients treated with SYMLIN and insulin and patients treated with insulin and placebo had equivalent reductions in mean HbA1c (-0.47 ± 0.07% vs. -0.49 ± 0.07%, respectively); patients on SYMLIN lost weight (-1.33 ± 0.31 kg relative to baseline and -2.6 kg relative to placebo plus insulin-treated patients). SYMLIN-treated patients used less total insulin (-11.7% relative to baseline) and less short/rapid-acting insulin (-22.8%) relative to baseline.

Open-Label Study in the Clinical Practice Setting. An open-label study of SYMLIN was conducted in patients with type 1 diabetes who were unable to achieve glycemic targets using insulin alone. A flexible-dose insulin regimen was employed in these patients after SYMLIN titration was completed (see DOSAGE and ADMINISTRATION). In this study, patients adjusted their insulin regimen based on pre- and post-meal glucose monitoring. At baseline, mean HbA1c was 8.0%, mean age was 42.7 years, mean duration of diabetes was 21.2 years, and mean BMI was 28.6 kg/m^2. SYMLIN daily dosage was 30 mcg or 60 mcg with major meals.

SYMLIN plus insulin reduced HbA1c and body weight from baseline at 6 months by a mean of 0.18% and 3.0 kg, respectively. These changes in glycemic control and body weight were achieved with reductions in doses of total, short-acting, and long-acting insulin (-12.0 ± 1.36, -21.7 ± 2.81, and -0.4 ± 1.59%, respectively).

INDICATIONS AND USAGE

SYMLIN is given at mealtimes and is indicated for:

- Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.
- Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.

CONTRAINDICATIONS

SYMLIN is contraindicated in patients with any of the following:

- a known hypersensitivity to SYMLIN or any of its components, including metacresol;
- a confirmed diagnosis of gastroparesis;
- hypoglycemia unawareness.

WARNINGS

Patient Selection

Proper patient selection is critical to safe and effective use of SYMLIN. Before initiation of therapy, the patient's HbA1c, recent blood glucose monitoring data, history of insulin-induced hypoglycemia, current insulin regimen, and body weight should be reviewed. SYMLIN therapy should only be considered in patients with insulin-using type 2 or type 1 diabetes who fulfill the following criteria:

- have failed to achieve adequate glycemic control despite individualized insulin management;
- are receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes educator(s).

Patients meeting any of the following criteria should NOT be considered for SYMLIN therapy:

- poor compliance with current insulin regimen;
- poor compliance with prescribed self-blood glucose monitoring;
- have an HbA1c >9%;
- recurrent severe hypoglycemia requiring assistance during the past 6 months;
- presence of hypoglycemia unawareness;
- confirmed diagnosis of gastroparesis;
- require the use of drugs that stimulate gastrointestinal motility;
- pediatric patients.

Hypoglycemia. SYMLIN alone does not cause hypoglycemia. However, SYMLIN is indicated to be co-administered with insulin therapy and in this setting SYMLIN increases the risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. Severe hypoglycemia associated with SYMLIN occurs within the first 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries may occur. Therefore, when introducing SYMLIN therapy, appropriate precautions need to be taken to avoid increasing the risk for insulin-induced severe hypoglycemia. These precautions include **frequent pre- and post-meal glucose monitoring combined with an initial 50% reduction in pre-meal doses of short-acting insulin (see DOSAGE and ADMINISTRATION)**.

Symptoms of hypoglycemia may include hunger, headache, sweating, tremor, irritability, or difficulty concentrating. Rapid reductions in blood glucose concentrations may induce such symptoms regardless of glucose values. More severe symptoms of hypoglycemia include loss of consciousness, coma, or seizure.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes; diabetic nerve disease; use of medications such as beta-blockers, clonidine, guanethidine, or reserpine; or intensified diabetes control.

The addition of any antihyperglycemic agent such as SYMLIN to an existing regimen of one or more antihyperglycemic agents (e.g., insulin, sulfonylurea), or other agents that can increase the risk of hypoglycemia may necessitate further insulin dose adjustments and particularly close monitoring of blood glucose.

The following are examples of substances that may increase the blood glucose-lowering effect and susceptibility to hypoglycemia: oral anti-diabetic products, ACE inhibitors, diisopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates, and sulfonamide antibiotics.

Clinical studies employing a controlled hypoglycemic challenge have demonstrated that SYMLIN does not alter the counter-regulatory hormonal response to insulin-induced hypoglycemia. Likewise, in SYMLIN-treated patients, the perception of hypoglycemic symptoms was not altered with plasma glucose concentrations as low as 45 mg/dL.

PRECAUTIONS

General

Hypoglycemia (See WARNINGS).

SYMLIN should be prescribed with caution to persons with visual or dexterity impairment.

Information for Patients: Healthcare providers should inform patients of the potential risks and advantages of SYMLIN therapy. Healthcare providers should also inform patients about self-management practices including glucose monitoring, proper injection technique, timing of dosing, and proper storage of SYMLIN. In addition, reinforce the importance of adherence to meal planning, physical activity, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. Refer patients to the SYMLIN Medication Guide and Patient Instructions for Use for additional information.

Instruct patients on handling of special situations such as intercurrent conditions (illness or stress), an inadequate or omitted insulin dose, inadvertent administration of increased insulin or SYMLIN dose, inadequate food intake or missed meals.

SYMLIN and insulin should always be administered as separate injections and never be mixed.

Women with diabetes should be advised to inform their healthcare professional if they are pregnant or contemplating pregnancy.

Renal Impairment: The dosing requirements for SYMLIN are not altered in patients with moderate or severe renal impairment (Cl_{cr} >20 to ≤50 mL/min). No studies have been done in dialysis patients (see CLINICAL PHARMACOLOGY; Special Populations).

Hepatic Impairment: Studies have not been performed in patients with hepatic impairment. However, hepatic dysfunction is not expected to affect blood concentrations of SYMLIN (see CLINICAL PHARMACOLOGY; Special Populations).

Allergy:
Local allergy. Patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than SYMLIN, such as irritants in a skin cleansing agent or improper injection technique.

Systemic Allergy. In controlled clinical trials up to 12 months, potential systemic allergic reactions were reported in 65 (5%) of type 2 patients and 59 (5%) of type 1 SYMLIN-treated patients. Similar reactions were reported by 18 (4%) and 28 (5%) of placebo-treated type 2 and type 1 patients, respectively. No patient receiving SYMLIN was withdrawn from a trial due to a potential systemic allergic reaction.

Drug Interactions

Due to its effects on gastric emptying, SYMLIN therapy should not be considered for patients taking drugs that alter gastrointestinal motility (e.g., anticholinergic agents such as atropine) and agents that slow the intestinal absorption of nutrients (e.g., α-glucosidase inhibitors). Patients using these drugs have not been studied in clinical trials.

SYMLIN has the potential to delay the absorption of concomitantly administered oral medications. When the rapid onset of a concomitant orally administered agent is a critical determinant of effectiveness (such as analgesics), the agent should be administered at least 1 hour prior to or 2 hours after SYMLIN injection.

In clinical trials, the concomitant use of sulfonylureas or biguanides did not alter the adverse event profile of SYMLIN. No formal interaction studies have been performed to assess the effect of SYMLIN on the kinetics of oral antidiabetic agents.

Mixing SYMLIN and Insulin

The pharmacokinetic parameters of SYMLIN were altered when mixed with regular, NPH, and 70/30 premixed formulations of recombinant human insulin immediately prior to injection. **Thus, SYMLIN and insulin should not be mixed and must be administered separately.**

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis. A two-year carcinogenicity study was conducted in CD-1 mice with doses of 0.2, 0.5, and 1.2 mg/kg/day of SYMLIN (32, 67, and 159 times the exposure resulting from the maximum recommended human dose based on area under the plasma concentration curve or AUC, respectively). No drug-induced tumors were observed. A two-year carcinogenicity study was conducted in Sprague-Dawley rats with doses of 0.04, 0.2, and 0.5 mg/kg/day of SYMLIN (3, 9, and 25 times the exposure resulting from the maximum recommended human dose based on AUC, respectively). No drug-induced tumors were observed in any organ.

Mutagenesis. SYMLIN was not mutagenic in the Ames test and did not increase chromosomal aberration in the human lymphocytes assay. SYMLIN was not clastogenic in the *in vivo* mouse micronucleus test or in the chromosomal aberration assay utilizing Chinese hamster ovary cells.

Impairment of Fertility. Administration of 0.3, 1, or 3 mg/kg/day of SYMLIN (8, 17, and 82 times the exposure resulting from the maximum recommended human dose based on body surface area) had no significant effects on fertility in male or female rats. The highest dose of 3 mg/kg/day resulted in dystocia in 8/12 female rats secondary to significant decreases in serum calcium levels.

Pregnancy

Teratogenic Effects: Pregnancy Category C. No adequate and well-controlled studies have been conducted in pregnant women. Studies in perfused human placenta indicate that SYMLIN has low potential to cross the maternal/fetal placental barrier. Embryofetal toxicity studies with SYMLIN have been performed in rats and rabbits. Increases in congenital abnormalities (neural tube defect, cleft palate, exencephaly) were observed in fetuses of rats treated during organogenesis with 0.3 and 1.0 mg/kg/day (10 and 47 times the exposure resulting from the maximum recommended human dose based on AUC, respectively). Administration of doses up to 0.3 mg/kg/day SYMLIN (9 times maximum recommended dose based on AUC) to pregnant rabbits had no adverse effects in embryofetal development; however, animal reproduction studies are not always predictive of human response. SYMLIN should be used during pregnancy only if it is determined by the healthcare professional that the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is unknown whether SYMLIN is excreted in human milk. Many drugs, including peptide drugs, are excreted in human milk. Therefore, SYMLIN should be administered to nursing women only if it is determined by the healthcare professional that the potential benefit outweighs the potential risk to the infant.

Pediatric Use

Safety and effectiveness of SYMLIN in pediatric patients have not been established.

Geriatric Use

SYMLIN has been studied in patients ranging in age from 15 to 84 years of age, including 539 patients 65 years of age or older. The change in HbA1c values and hypoglycemia frequencies did not differ by age, but greater sensitivity in some older individuals cannot be ruled out. Thus, both SYMLIN and insulin regimens should be carefully managed to obviate an increased risk of severe hypoglycemia.

ADVERSE REACTIONS

Adverse events (excluding hypoglycemia, discussed below) commonly associated with SYMLIN when co-administered with a fixed dose of insulin in the long-term, placebo-controlled trials in insulin-using type 2 patients and type 1 patients are presented in **Table 4** and **Table 5**, respectively. The same adverse events were also shown in the open-label clinical practice study, which employed flexible insulin dosing.

Table 4: Treatment-Emergent Adverse Events Occurring With ≥5% Incidence and Greater Incidence With SYMLIN Compared With Placebo in Long-Term, Placebo-Controlled Trials. Incidence of the Same Events in the Open-Label Clinical Practice Study (Patients With Insulin-Using Type 2 Diabetes, 120 mcg)

	Long-Term, Placebo-Controlled Studies		Open-Label, Clinical Practice Study
	Placebo + Insulin (n(%)) (N=284)	SYMLIN + Insulin (n(%)) (N=292)	SYMLIN + Insulin (n(%)) (N=166)
Nausea	34 (12)	81 (28)	53 (30)
Headache	19 (7)	39 (13)	8 (5)
Anorexia	5 (2)	27 (9)	1 (<1)
Vomiting	12 (4)	24 (8)	13 (7)
Abdominal Pain	19 (7)	23 (8)	3 (2)
Fatigue	11 (4)	20 (7)	5 (3)
Dizziness	11 (4)	17 (6)	3 (2)
Coughing	12 (4)	18 (6)	4 (2)
Pharyngitis	7 (2)	15 (5)	6 (3)

Table 5: Treatment-Emergent Adverse Events Occurring With ≥5% Incidence and Greater Incidence With SYMLIN Compared to Placebo in Long-Term, Placebo-Controlled Studies. Incidence of the Same Events in the Open-Label Clinical Practice Study (Patients With Type 1 Diabetes, 30 or 60 mcg)

	Long-Term, Placebo-Controlled Studies		Open-Label, Clinical Practice Study
	Placebo + Insulin (n(%)) (N=538)	SYMLIN + Insulin (n(%)) (N=716)	SYMLIN + Insulin (n(%)) (N=265)
Nausea	92 (17)	342 (48)	98 (37)
Anorexia	12 (2)	122 (17)	0 (0)
Inflicted Injury	55 (10)	97 (14)	20 (8)
Vomiting	36 (7)	82 (11)	18 (7)
Arthralgia	27 (5)	51 (7)	6 (2)
Fatigue	22 (4)	51 (7)	12 (4.5)
Allergic Reaction	28 (5)	41 (6)	1 (<1)
Dizziness	21 (4)	34 (5)	5 (2)

Most adverse events were gastrointestinal in nature. In patients with type 2 or type 1 diabetes, the incidence of nausea was higher at the beginning of SYMLIN treatment and decreased with time in most patients. The incidence and severity of nausea are reduced when SYMLIN is gradually titrated to the recommended doses (see DOSAGE and ADMINISTRATION).

Severe Hypoglycemia

SYMLIN alone (without the concomitant administration of insulin) does not cause hypoglycemia. However, SYMLIN is indicated as an adjunct treatment in patients who use mealtime insulin therapy and co-administration of SYMLIN with insulin can increase the risk of insulin-induced hypoglycemia, particularly in patients with type 1 diabetes (see Boxed Warning). The incidence of severe hypoglycemia during the SYMLIN clinical development program is summarized in **Table 6** and **Table 7**.

Table 6: Incidence and Event Rate of Severe Hypoglycemia in Long-Term, Placebo-Controlled and Open-Label, Clinical Practice Studies in Patients With Insulin-Using Type 2 Diabetes

	Long-Term, Placebo-Controlled Studies (No Insulin Dose-Reduction During Initiation)				Open-Label, Clinical Practice Study (Insulin Dose-Reduction During Initiation)	
	Placebo + Insulin		SYMLIN + Insulin		SYMLIN + Insulin	
Severe Hypoglycemia	0-3 Months (n=284)	>3-6 Months (n=251)	0-3 Months (n=292)	>3-6 Months (n=255)	0-3 Months (n=166)	>3-6 Months (n=150)
Patient-Ascertained*						
Event Rate (event rate/ patient year)	0.24	0.13	0.45	0.39	0.05	0.03
Incidence (%)	2.1	2.4	8.2	4.7	0.6	0.7
Medically Assisted**						
Event Rate (event rate/ patient year)	0.06	0.07	0.09	0.02	0.05	0.03
Incidence (%)	0.7	1.2	1.7	0.4	0.6	0.7

* Patient-ascertained severe hypoglycemia: Requiring the assistance of another individual (including aid in ingestion of oral carbohydrate); and/or requiring the administration of glucagon injection, intravenous glucose, or other medical intervention.

** Medically assisted severe hypoglycemia: Requiring glucagon, IV glucose, hospitalization, paramedic assistance, emergency room visit, and/or assessed as an SAE by the investigator.

Table 7: Incidence and Event Rate of Severe Hypoglycemia in Long-Term, Placebo-Controlled and Open-Label, Clinical Practice Studies in Patients With Type 1 Diabetes

	Long-Term, Placebo-Controlled Studies (No Insulin Dose-Reduction During Initiation)				Open-Label, Clinical Practice Study (Insulin Dose-Reduction During Initiation)	
	Placebo + Insulin		SYMLIN + Insulin		SYMLIN + Insulin	
Severe Hypoglycemia	0-3 Months (n=538)	>3-6 Months (n=470)	0-3 Months (n=716)	>3-6 Months (n=576)	0-3 Months (n=265)	>3-6 Months (n=213)
Patient-Ascertained*						
Event Rate (event rate/ patient year)	1.33	1.06	1.55	0.82	0.29	0.16
Incidence (%)	10.8	8.7	16.8	11.1	5.7	3.8
Medically Assisted**						
Event Rate (event rate/ patient year)	0.19	0.24	0.50	0.27	0.10	0.04
Incidence (%)	3.3	4.3	7.3	5.2	2.3	0.9

* Patient-ascertained severe hypoglycemia: Requiring the assistance of another individual (including aid in ingestion of oral carbohydrate); and/or requiring the administration of glucagon injection, intravenous glucose, or other medical intervention.

** Medically assisted severe hypoglycemia: Requiring glucagon, IV glucose, hospitalization, paramedic assistance, emergency room visit, and/or assessed as an SAE by the investigator.

Post Marketing Experience

Since market introduction of SYMLIN, the following adverse reactions have been reported. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General: Injection site reactions.

OVERDOSAGE

Single 10 mg doses of SYMLIN (83 times the maximum dose of 120 mcg) were administered to three healthy volunteers. Severe nausea was reported in all three individuals and was associated with vomiting, diarrhea, vasodilatation, and dizziness. No hypoglycemia was reported. SYMLIN has a short half-life and in the case of overdose, supportive measures are indicated.

DOSAGE AND ADMINISTRATION

SYMLIN dosage differs depending on whether the patient has type 2 or type 1 diabetes (see below). When initiating therapy with SYMLIN, initial insulin dose reduction is required in all patients (both type 2 and type 1) to reduce the risk of insulin-induced hypoglycemia. As this reduction in insulin can lead to glucose elevations, patients should be monitored at regular intervals to assess SYMLIN tolerability and the effect on blood glucose, so that **individualized** insulin adjustments can be initiated. If SYMLIN therapy is discontinued for any reason (e.g., surgery or illnesses), the same initiation protocol should be followed when SYMLIN therapy is re-instituted (see below).

Initiation of SYMLIN therapy

Patients With Insulin-Using Type 2 Diabetes

In patients with insulin-using type 2 diabetes, SYMLIN should be initiated at a dose of 60 mcg and increased to a dose of 120 mcg as tolerated.

Patients should be instructed to:

- Initiate SYMLIN at 60 mcg subcutaneously, immediately prior to major meals;
- Reduce preprandial, rapid-acting or short-acting insulin dosages, including fixed-mix insulins (70/30) by **50%**;
- Monitor blood glucose frequently, including pre- and post-meals and at bedtime;
- Increase the SYMLIN dose to the next increment (30 mcg, 45 mcg, or 60 mcg) when no clinically significant nausea has occurred for at least 3 days. **SYMLIN dose adjustments should be made only as directed by the healthcare professional.** If significant nausea persists at the 45 or 60 mcg dose level, the SYMLIN dose should be decreased to 30 mcg. If the 30 mcg dose is not tolerated, discontinuation of SYMLIN therapy should be considered;
- Adjust insulin doses to optimize glycemic control once the target dose of SYMLIN is achieved and nausea (if experienced) has subsided. **Insulin dose adjustments should be made only as directed by the healthcare professional;**
- Contact a healthcare professional skilled in the use of insulin to review SYMLIN and insulin dose adjustments at least once a week until a target dose of SYMLIN is achieved, SYMLIN is well-tolerated, and blood glucose concentrations are stable.

Patients With Type 1 Diabetes

In patients with type 1 diabetes, SYMLIN should be initiated at a dose of 15 mcg and titrated at 15-mcg increments to a maintenance dose of 30 mcg or 60 mcg as tolerated.

Patients should be instructed to:

- Initiate SYMLIN at a starting dose of 15 mcg subcutaneously, immediately prior to major meals;
- Reduce preprandial, rapid-acting or short-acting insulin dosages, including fixed-mix insulins (e.g., 70/30) by **50%**;
- Monitor blood glucose frequently, including pre- and post-meals and at bedtime;
- Increase the SYMLIN dose to the next increment (30 mcg, 45 mcg, or 60 mcg) when no clinically significant nausea has occurred for at least 3 days. **SYMLIN dose adjustments should be made only as directed by the healthcare professional.** If significant nausea persists at the 45 or 60 mcg dose level, the SYMLIN dose should be decreased to 30 mcg. If the 30 mcg dose is not tolerated, discontinuation of SYMLIN therapy should be considered;
- Adjust insulin doses to optimize glycemic control once the target dose of SYMLIN is achieved and nausea (if experienced) has subsided. **Insulin dose adjustments should be made only as directed by the healthcare professional;**
- Contact a healthcare professional skilled in the use of insulin to review SYMLIN and insulin dose adjustments at least once a week until a target dose of SYMLIN is achieved, SYMLIN is well-tolerated, and blood glucose concentrations are stable.

Once Target Dose of SYMLIN is Achieved in Type 2 or Type 1 Patients

After a maintenance dose of SYMLIN is achieved, both insulin-using patients with type 2 diabetes and patients with type 1 diabetes should be instructed to:

- Adjust insulin doses to optimize glycemic control once the target dose of SYMLIN is achieved and nausea (if experienced) has subsided. **Insulin dose adjustments should be made only as directed by a healthcare professional;**
- Contact a healthcare professional in the event of recurrent nausea or hypoglycemia. An increased frequency of mild to moderate hypoglycemia should be viewed as a warning sign of increased risk for severe hypoglycemia.

Administration

SYMLIN should be administered subcutaneously immediately prior to each major meal (≥250 kcal or containing ≥30 g of carbohydrate).

SYMLIN should be at room temperature before injecting to reduce potential injection site reactions. Each SYMLIN dose should be administered subcutaneously into the abdomen or thigh (administration into the arm is not recommended because of variable absorption). Injection sites should be rotated so that the same site is not used repeatedly. The injection site selected should also be distinct from the site chosen for any concomitant insulin injection.

- **SYMLIN and insulin should always be administered as separate injections.**
- **SYMLIN should not be mixed with any type of insulin.**
- **If a SYMLIN dose is missed, wait until the next scheduled dose and administer the usual amount.**

SymlinPen® pen-injector

The SymlinPen® pen-injector is available in two presentations:

- SymlinPen® 60 pen-injector for doses of 15 mcg, 30 mcg, 45 mcg and 60 mcg.
- SymlinPen® 120 pen-injector for doses of 60 mcg and 120 mcg.

See the accompanying Patient Instructions for Use for instructions for using the SymlinPen® pen-injector.

The patient should be advised:

- to confirm they are using the correct pen-injector that will deliver their prescribed dose;
- on proper use of the pen-injector, emphasizing how and when to set up a new pen-injector;
- **not to transfer SYMLIN from the pen-injector to a syringe. Doing so could result in a higher dose than intended, because SYMLIN in the pen-injector is a higher concentration than SYMLIN in the SYMLIN vial;**
- not to share the pen-injector and needles with others;
- that needles are not included with the pen-injector and must be purchased separately;
- which needle length and gauge should be used;
- to use a new needle for each injection.

SYMLIN vials

To administer SYMLIN from vials, use a U-100 insulin syringe (preferably a 0.3 mL [0.3 cc] size) for optimal accuracy. If using a syringe calibrated for use with U-100 insulin, use the chart below **(Table 8)** to measure the microgram dosage in unit increments.

Table 8: Conversion of SYMLIN Dose to Insulin Unit Equivalents

Dosage Prescribed (mcg)	Increment Using a U-100 Syringe (Units)	Volume (cc or mL)
15	2½	0.025
30	5	0.05
45	7½	0.075
60	10	0.1
120	20	0.2

Always use separate, new syringes and needles to give SYMLIN and insulin injections.

Discontinuation of Therapy

SYMLIN therapy should be discontinued if any of the following occur:

- Recurrent unexplained hypoglycemia that requires medical assistance;
- Persistent clinically significant nausea;
- Noncompliance with self-monitoring of blood glucose concentrations;
- Noncompliance with insulin dose adjustments;
- Noncompliance with scheduled healthcare professional contacts or recommended clinic visits.

Preparation and Handling

SYMLIN should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and the container permit.

HOW SUPPLIED

SYMLIN is supplied as a sterile injection in the following dosage forms:

- 1.5 mL disposable multidose SymlinPen® 60 pen-injector containing 1000 mcg/mL pramlintide (as acetate).
- 2.7 mL disposable multidose SymlinPen® 120 pen-injector containing 1000 mcg/mL pramlintide (as acetate).
- 5 mL vial, containing 600 mcg/mL pramlintide (as acetate), for use with an insulin syringe.

To administer SYMLIN from vials, use a U-100 insulin syringe (preferably a 0.3 mL [0.3 cc] size). If using a syringe calibrated for use with U-100 insulin, use the chart **(Table 8)** in the DOSAGE AND ADMINISTRATION section to measure the microgram dosage in unit increments.

Do not mix SYMLIN with insulin.

SYMLIN Injection is available in the following package sizes:

- SymlinPen® 60 pen-injector, containing 1000 mcg/mL pramlintide (as acetate) 2 X 1.5 mL disposable multidose pen-injector (NDC 66780-115-02)
- SymlinPen® 120 pen-injector, containing 1000 mcg/mL pramlintide (as acetate) 2 X 2.7 mL disposable multidose pen-injector (NDC 66780-121-02)
- 5 mL vial, containing 600 mcg/mL pramlintide (as acetate), for use with an insulin syringe (NDC 66780-110-01)

STORAGE

SYMLIN pen-injectors and vials not in use: Refrigerate (36°F to 46°F; 2°C to 8°C), and protect from light. Do not freeze. Do not use if product has been frozen. Unused SYMLIN (opened or unopened) should not be used after the expiration (EXP) date printed on the carton and the label.

SYMLIN pen-injectors and vials in use: After first use, refrigerate or keep at a temperature not greater than 86°F (30°C) for 30 days. Use within 30 days, whether or not refrigerated.

Storage conditions are summarized in **Table 9**.

Table 9: Storage Conditions

Dosage Form	Unopened (not in use) Refrigerated	Open (in use) Refrigerated or Temperature Up To 86°F (30°C)
1.5 mL pen-injector 2.7 mL pen-injector 5 mL vial	Until Expiration Date	Use Within 30 Days

The SymlinPen® pen-injectors and SYMLIN vials are manufactured for:
Amylin Pharmaceuticals, Inc.
San Diego, CA 92121 USA
1-800-349 8919
http://www.SYMLIN.com

Rx only

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